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IN HONOUR OF

TAGE KEMP

ON HIS SIXTIETH BIRTHDAY

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OF TAGE KEMP

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MONGOLOID TWINS AND THEIR SIBLINGS[1]

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The dependence of mongolism (congenital acromicria) on maternal age is well established. Less certain, though generally conceded, is the association of the condition with maternal ill health preceding or during gestation. Most of the evidence for maternal ill health is related to the female reproductive system, notably to impaired fertility and abortion. It is also known, from the embryologically primitive structures which are altered in mongolism, that development of the embryo is abnormal as early as the ninth week (*Ingalls* [1947]), and possibly much earlier. In *Benda*'s opinion [1949], the cause of mongolism will be found "in the condition of the mother at the beginning of the pregnancy." According to *Øster* [1953], mongolism "probably has its cause in exogenous factors related to the mother's depressed reproductive faculty."

Clinically, it is rather difficult to distinguish between influences acting on the ovum or zygote before cleavage and those acting on the early embryo. Continued menstruation after conception may exert an abnormal influence on the embryo's development, but it may also indicate that the ovum was formed and liberated in an abnormal ovarian environment. The long period of enforced sterility frequently preceding the conception of a mongoloid child suggests an abnormal ovary even more strongly than it does an abnormal uterine environment.

Twin data assembled from the literature have repeatedly been

[1] Prepared as a contribution to the Anniversary Number for Prof. *Tage Kemp* on behalf of the research staff of the Department of Medical Genetics of the New York State Psychiatric Institute (*Franz J. Kallmann*, M.D.), this report is part of a study of mentally defective twins, conducted jointly by this department and the Laboratory of Socio-environmental Studies, National Institute of Mental Health, Public Health Service, United States Department of Health, Education, and Welfare.

cited as evidence on the etiology of mongolism, but cannot be regarded as statistically representative. In order to obtain a consecutive series of affected twins, routine reporting of twins admitted to New York State Schools[1] for mental defectives was organized by Dr. *Kallmann* in 1937. Among 645 twins so ascertained, 32 were mongoloids. In addition, seven twin mongoloids came to our attention as referred clinic cases and can be included in the analysis where a representative sample of index cases is not essential. This sample affords a new opportunity to investigate several questions which have been raised in connection with the etiology of mongolism. All of them are relevant to the time and mode of action of the adverse maternal environment and may be formulated as follows:

1. Does a twin pregnancy carry with it an increased (or diminished) risk of mongolism?
2. Are monozygotic and dizygotic twin subjects equally prone to mongolism?
3. Are monozygotic twins ever discordant with respect to mongolism? In other words, does a mongoloid child ever have a normal monozygotic twin partner?
4. When one member of a dizygotic pair is mongoloid, is the second member more likely or less likely to be affected than are siblings born to the same mother in subsequent pregnancies?
5. When only one member of a twin pair is mongoloid, does the cotwin carry any stigmata that can be attributed to the same cause as his partner's mongolism?

1. The Index Pairs

Of the 33 twin index pairs included in the present series (table 1), five are known to have been previously reported in the literature as either concordant or discordant for mongolism (*Frumkin* [1935], *Jervis* [1943], *Kallmann* [1953], *Rogers* and *Allen* [1955]). Another pair (No. 27) will be used in a later publication on reciprocal skin homografting.

In 25 cases it was possible to confirm the hospital diagnosis by personal examination of the patient. One diagnostically questionable pair of twins, both affected, was excluded from the series. One

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[1] The authors are grateful to the directors and staffs of the State Schools for their splendid cooperation in the conduct of this research.

Table 1. Summary of Case Material.

Case Number		Index Case			Cotwin		Siblings Studied
Serial	Reference	Age **	Zygosity	Sex	Sex	Comments	
*1	PI 2	28	MZ	F	F	Case 2	
*2	PI 3	28	MZ	F	F	Case 1	
*3	PI 5	26	DZ	M	M		3
*4	L 604	(dead)	?	M	M	Case 5	
*5	L 605	(dead)	?	M	M	Case 4	
6	Wa 814	31	?	M	M	uncooperative	
7	L 866	—	DZ	M	F	contact lost	
8	R 1054	(dead)	DZ	M	F		1
9	R 1291	—	DZ	M	F	contact lost	
10	Wi 1528	12	DZ	M	F		2
*11	R 1550	8	MZ	M	M	Case 12	
*12	R 1551	8	MZ	M	M	Case 11	
13	Wi 1554	8	DZ	M	F		3
14	Wi 1583	(dead)	DZ	F	M	Negro, contact lost	
15	Wi 1698	—	DZ	M	F	contact lost	
16	L 1963	26	DZ	F	M		7
17	L 1973	10	DZ	M	F		3
*18	L 1994	10	DZ	M	M		3
19	L 2031	—	DZ	M	F	died at 3 days	
20	L 2059	15	DZ	M	M		4
21	PI 2111	—	DZ	F	M	contact lost	
22	PI 2124	2	DZ	M	M	musc. dystrophy age 3	2
23	N 2133	13	DZ	F	M		1
24	N 2140	8	DZ	F	M		1
25	N 2144	11	DZ	M	M		1
26	Wa 2153	16	DZ	F	M		1
27	Wa 2156	8	DZ	F	F	quadruplets, 2 b. dead	
28	N 2172	(dead)	?	F	F	Case 29	
29	N 2173	(dead)	?	F	F	Case 28	
30	Wa 2179	11	TZ	F	M, M	triplets	1
31	R 2327	9	DZ	M	M	microcephalic	2
32	R 2350	(dead)	?	F	F	contact lost	
33	Wi 2366	16	DZ	F	F		
34	Wi 2369	2	DZ	M	F		2
35	PI 2373	3	MZ	M	M	Case 36	
36	PI 2374	3	MZ	M	M	Case 35	
37	Wi 2392	(dead)	?	M	M	Case 38	
38	Wi 2393	(dead)	?	M	M	Case 37	
39	Wi 2482	—	?	F	F	infant	

* Reports on these cases previously published.

** Ages given are at time of examination. Others were not examined.

Fig. 1. Monozygotic mongoloid twins, Cases 35 and 36.

institutionalized twin patient classified as hydrocephalic was found on examination to be mongoloid as well.

Of the 32 cases collected from State Schools, eight form four concordant pairs, and 23 are known to have had nonmongoloid partners. The cotwin of the remaining case died three days after birth and was described by the mother as having been normal. Nevertheless, this pair is omitted in table 3 and will be excluded from discussions dealing with problems of concordance. Of the seven cases ascertained through sources other than State Schools, four represent two concordant pairs, and three are known to have nonmongoloid cotwins.

2. *Determination of Zygosity*

For the separation of same-sex pairs into monozygotic (MZ) and dizygotic (DZ) categories, *blood group data* were supplemented or confirmed by quantitative analysis of the fingerprints and by comparison of hair and eye pigmentation and ear lobe form. Other morphological traits and metric characters were considered unreliable in twins discordant for grossly pathological features. Blood typing was done in three steps for reasons of economy. All same-sex pairs were grouped and typed with the major ABO and Rh antisera. In pairs found to be similar in these factors, the testing was continued either until a difference appeared or until all factors had been determined with antisera available at the Blood Bank of the

Table 2. Results of Blood Typing in Same-Sex Pairs.

Concordant Pairs	A	(A_2)	B	D	C	E	c	e	M	N	Fy^a	K	Le^a	S	s	P	Jk^a
Twin Pairs																	
1, 2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
11, 12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
35, 36	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4, 5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Discordant Pairs																	
22	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
31	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
33	— —	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
27	— —	[illegible]	[illegible]	+ [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
18*	[illegible]	[illegible]	[illegible]	[illegible] +	+ [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
25*	— —	[illegible]	[illegible]	[illegible] +	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* Dizygosity confirmed through skin grafts.

Columbia-Presbyterian Medical Center[1]. In some cases, additional tests were made by the Knickerbocker Foundation or by Dr. *Philip Levine* of the Ortho Research Foundation. The blood typing data are summarized in table 2.

In the *dermatoglyphic analysis*, only fingerprints were used for the purpose of twin diagnosis. The fingerprints of twin partners discordant as to mongolism may show some differences in connection with the pathological changes in the affected twin (*Cummins* [1939]). However, compared with the usual intra-pair differences in dizygotic twins, statistical abnormalities of mongoloid fingerprints are not so pronounced as to preclude the use of ordinary zygosity criteria, especially in pairs concordant for the condition.

The three measures used in the analysis of fingerprints are fairly objective in that they are based on observations made separately on each twin rather than on direct comparisons. The simplest one is the sum of the two homolateral ridge-count differences (*Ford* and *Frumkin* [1942]), in which fingers with whorl patterns are represented only by the higher count. A difference of more than 40 is strongly suggestive or dizygosity.

Another measuring device of almost equal simplicity is *Wendt*'s individual pattern score or *Musterwert* [1955]. In this procedure, each pattern is classified according to more or less objective criteria and scored from one to seven. A difference of more than five in the total score of twins can be regarded as nearly conclusive evidence of dizygosity.

The most complex test is *Slater*'s discriminant function [1953], which is computed from all ridge counts. A score greater than two is fairly conclusive evidence of dizygosity, and a score below minus one is suggestive of monozygosity.

There is no reason to believe that the rate or quantity of pigment formation is affected in mongolism. It is generally true of twins, however, that pigmentation differences are inconclusive unless they are very distinct. Minor differences in hair color as well as slight quantitative or qualitative differences in iris pigmentation may occur in apparently monozygotic twins.

In this study, *eye color* was recorded according to a simplification of *Brues*' method [1946], which requires separate notation of the color of the background (blue, green or brown) and of the detail or surface of the iris (gray, yellow, orange or brown). Quantitative difference in detail area, although noted during the examinations, did not prove useful in this series of twins.

Ear lobe form was differentiated as either free or attached. Since mongoloids have small ear lobes, this distinction was not always easy to make. In fact, a significant difference in this feature was observed in only two pairs.

Death or unavailability of one or both twins prevented zygosity determination in nine cases among the same-sex pairs. The data obtained on the other 12 same-sex cases were sufficient for diagnostic purposes and are summarized in tables 4 and 5. In this same-sex series (table 3), 12 cases formed six concordant pairs, two of which died before comprehensive studies could be arranged. First-hand

[1] The authors wish to thank the Blood Bank staff and especially Miss *Erika Awer* for much time and care devoted to blood typing in our various twin studies.

Table 3. Summary of Index Cases in Terms of Zygosity and Concordance*

	Institutional Series		Special Cases		Total
	Concordant	Discordant	Concordant	Discordant	
Monozygotic	2	0	4	0	6
Dizygotic: Same-sex	0	6	0	2	8
Opposite-sex	0	14	0	1	15
Unknown Zygosity	6	3	0	0	9
Total	8	23	4	3	38

* Mongoloid patients with mongoloid cotwins are referred to as concordant, or as belonging to concordant pairs. Since in all concordant pairs both twins were found together, each such pair is represented in this table by two cases.

data were obtained in three concordant pairs and proved entirely consistent with monozygosity.

One concordant same-sex pair (cases 4 and 5) was no longer alive when the present study was begun, but both twins were extensively studied by another investigator (*Jervis* [1943]). Their fingerprints, which are still available, are consistent with a diagnosis of monozygosity. Other similarities extended to stature, general appearance and intelligence quotients. The eye color of the twins was originally described as "bright blue". It may be assumed that the difference in eye color later noted by *Jervis* applied to a limited area of surface (detail) pigment. Additional reasons for the dizygotic classification were (1) a report of separate placentas, (2) a qualitative comparison of fingerprints that indicated significant difference, and (3) the presence of a heart defect in only one twin. Since these differences are not sufficient to substantiate a diagnosis of dizygosity, it would seem advisable to place this pair in the category of uncertain zygosity.

Of 26 pairs known to be discordant, 15 were of opposite sex and hence dizygotic. This group includes one female of a set of triplets (case 30), whose two male partners differed in blood groups (DCe DcE). In three of the same-sex pairs one partner was dead or otherwise inaccessible. Of the remaining eight same-sex pairs, five showed blood factor differences with the standard battery of antisera (ABO, Rh, MN and Duffy). In each of these five twin pairs, dizygosity was also demonstrated by dermatoglyphic criteria or by a significant eye color difference. The dermatoglyphic data given for case 3 probably understate the actual difference in this pair. Because one

Table 4. Zygosity Data on Twin Pairs that were Similar in the Major Blood Factors.

Observation	Concordant				Discordant		
	1, 2	4, 5	11, 12	35, 36	18	25	27
Blood Factors	similar	similar	similar	similar	similar	similar	**different (P)**
Ridge Count Dif.	14	12	6	23	33	**49**	13
Wendt's Score	55/56	41/40	40/41	48/49	48/49	**50/43**	54/50
Slater's Function	—1.19	—2.36	—2.21	—2.15	—1.30	—0.63	—0.91
Hair Color	close	close	same	same	close	**light/dark**	same
Eye Color	bl-ye	**"br"/"gr"**	bl-gr	bl ye	**bl br/bl-gr**	bl-gr	**bl-gr/bl-ye**
Stature* (cm)	141/139	99/96.5	91/93	98.5/96	125/142	133/169	112/138
Head Length (mm)	159/159	—	158/160	161/160	165/185	168/187	157/176
Head Width (mm)	142/143	—	132/132	128/130	140/148	142/146	135/141
Ear Height (mm)	52/50.5	—	46.5/47	49.5/48	50/61	49/64.5	46/62
Ear Lobe	att.	(same)	att.	free	free	free	free
I.Q.*	28/27	47/47	37/34	41/46	29/105	24/?	24/90
Skin Grafts	—	—	—	—	**rejected**	—	**rejected**

* Stature and I.Q. were not in all instances obtained at the age shown in Table 1.

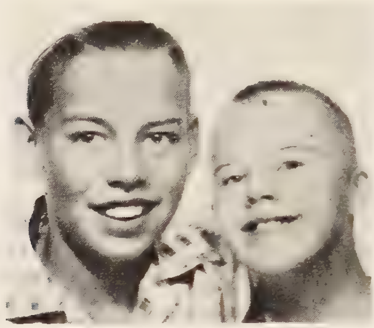

Fig. 2. Mongoloid with normal twin partner, considered dizygotic because of hair color and dermatoglyphic differences. Case 25.

Fig. 3. Mongoloids with normal twin partners proved dizygotic by skin grafts. Case 27 above and case 18 below.

Table 5. Zygosity Data on Twin Pairs that differed in the Major Blood Factors.

Observation	3	20	22	31	33
Blood Difference	**Rh_1Rh_2/Rh_1**	**N/M**	**Rh_1Rh_2/Rh_1**	**A/O**	**M/N, Fy^a—/+**
Ridge Count Dif.	13	20	**46**	16	5
Wendt's Score	40/45	45/41	40/38	**45/51**	**61/69**
Slater's Function	—1.66	—1.12	+**2.53**	—0.88	+**7.17**
Hair Color	same	close	same	? light/medium	close
Eye Color	**bl–ye/gr–or**	bl–ye/bl–gr	**br–br/gr–br**	**gr–br/bl–ye**	bl–ye
Stature* (cm)	156/170	125/175	82/88	121/122	136/160
Head Length (mm)	181/201	164/190	152/172	153/164	168/182
Head Width (mm)	151/166	140/149	129/134	131/137	137/148
Ear Height (mm)	57/65.5	46/64.5	44/48.5	52/63.5	50.5/64.5
Ear Lobe	free	**free/att.**	free	free	**att./free**
I.Q.*	17/97	36/94	?/103	33/70	32/?

* Stature and I.Q. were not in all instances obtained at the age shown in Table 1.

finger had been amputated and another scarred, it had to be assumed that they had the same patterns and counts as the corresponding fingers of the cotwin.

Of the three discordant pairs who were similar in all the usual blood tests (table 4), case 25 and his partner had a marked hair color difference and two dermatoglyphic characteristics that placed them among dizygotic twins. Additional antisera failed to differentiate their blood. Case 27 and her twin had a suggestive but indecisive eye color difference. Further blood typing revealed a difference in the P factor, and full-thickness skin homografts were rejected after initial takes lasting three and four weeks. The last pair, case 18, was the only one of the three whose Slater function strongly suggested monozygosity. However, this pair had a rather large difference in ridge counts and a significant eye color difference. Additional antisera failed to differentiate the blood, but reciprocal skin grafts were rejected after an initial take, at least in the normal cotwin; the mongoloid injured his graft so that the result was indeterminate.

3. *Frequency of Mongolism in Twins*

Morbidity data can usually be referred to the general population if obtained on a well defined group of patients. Two useful estimates can be obtained in this instance from the institutionalized mental

defectives: (1) the absolute frequency of twins among the institutionalized mongoloids, which can be compared with the frequency of twins in the total population and with the frequency of twins among other defectives; (2) the relative frequency of mongolism among institutionalized twins and nontwins. For both of these estimates ascertainment of index cases in the institutional population should be nearly complete and quite representative. Ascertainment can be evaluated by comparing the observed proportion of twins with figures obtained in other studies and by comparing subsamples within the present study.

In an investigation of 1107 retarded children in Baltimore, *Lilienfeld* and *Pasamanick* [1956] found 3.2 per cent of twins (standard error 0.75 per cent). *Looft* [1931] found two per cent of twins among registered defectives in Norway, and 3.6 per cent among borderline school children.

In the New York State population, a frequency of 3.1 $\pm$ .25 per cent was observed among admissions to five of the six State Schools in 1948–1951 (*Allen* and *Kallmann* [1955]). Eleven of the mongoloids in this series were among the twins reported for those schools and years. An additional 12 cases, including two concordant pairs, were reported in the larger subsample described in table 6. These two subsamples are compared in table 7, together with the State School patients who were admitted earlier or later. While there is an obvious difference between the first two subsamples, both groups were ascertained in the same manner. Changes in the

Table 6. Admissions to New York State Schools from April 1, 1947, to March 31, 1955.

Clinical Classification	Total Admissions		Reported Twins		Proportion of Twins in Per Cent
	Number	Per Cent	Number	Per Cent	
Undifferentiated	4611	38.2	94	28.2	2.59*
Familial	2986	24.7	103	31.0	
Mongolism	1177	9.8	23	6.9	1.95
Cranial Anomaly	741	6.2	21	6.3	2.83
Cerebral Palsy	596	4.9	23	6.9	3.86
Post-infectional	414	3.4	4	1.2	0.97
Post-traumatic	797	6.6	40	12.0	5.02
Miscellaneous	744	6.2	25	7.5	3.36
Total	12 066	100.0	333	100.0	2.76

* Some institutions diagnose concordant twins as "familial" who individually would be regarded as "undifferentiated".

Table 7. Comparison of State School Subsamples.

	Subsample Containing Highest Proportion of Twins	Additional Cases in Table 6	All Other State School Cases	Total
All Mongoloid Patients Admitted	462	715	(indefinite)	
Same-sex Cases, Concordant	0	4	4	8
Same-sex Cases, Discordant	2	3	4	9
Opposite-sex Cases	9	3	3	15
Total	11	12	13	32
Twins Among All Admissions in Per Cent	2.4	1.7	less than 1.0	

distribution of sex and concordance, if due to incomplete ascertainment, would be expected to produce the greatest disparity between the second and third samples, but these are almost identical. Chi-square (χ^2) for the table as a whole is 6.5 and not significant[1]. When the data are compressed into a fourfold table in which the third sample is compared with the first two, with respect to the proportion of opposite-sex pairs, χ^2 is only 1.7. A similar fourfold table that separates the first subsample from the other two yields a significant χ^2 of 5.8. If any part of this discrepancy is due to incomplete ascertainment, one would conclude that, in the total sample, opposite-sex pairs may be underrepresented while concordant pairs are most fully reported.

The frequency of twins among the mongoloid admissions was 1.95 per cent, with 95% confidence limits at 1.2 and 2.8 per cent. The observed frequency is a little lower than that for mental defectives in general, but it is close to the frequency of 1.9 per cent expected in the general population after the age of one year (*Allen* [1955]). The expected figure must be revised, however, to allow for the increased frequency of twinning with older maternal ages, in which most mongoloids occur[2]. The extent of this effect, as shown by the two figures in the next-to-last line of table 8, is rather small. A twin birth frequency of 1.1 per cent in the general population is

[1] Since reports are made on pairs of twins, concordant pairs are counted only once in the tests for sampling bias.

[2] The present series of mongoloids includes one Negro. In table 8 the distribution of mongoloids by maternal age includes all races, while the twin frequency data are based on whites only. The resulting error is probably inconsequential.

comparable to a frequency of 1.26 for mongoloids when maternal age is taken into account. The same ratio can be carried over to babies surviving the first year of life on the assumption that the mortality of mongoloid twins is proportionately as excessive as that of other twins. The twin frequency of 1.9 per cent for the general population thus becomes 2.2 for mongoloids. In the present study 2.4 per cent was the highest figure, obtained in the first subsample of table 8, and 1.95 is a more reliable estimate. This gives no indication of an increased rate of twinning in mongoloid pregnancies.

The second measure of association between twinning and mongolism is the relative frequency of mongolism among the reported twins. Incomplete ascertainment of twins cannot have much influence on this frequency. Mongoloids have a better socio-cultural background than the average defective, and their twin status is more likely to be known and reported. The figures in table 6 show a frequency among the nontwin defectives of 9.8 per cent mongoloids, and among the twins, 6.9 per cent. It is therefore unlikely that twins are any more susceptible to mongolism than are nontwins.

4. *Relative Susceptibility of MZ and DZ Twins to Mongolism*

Before concordance rates in MZ and DZ twins can be compared, some assurance is needed that the two types of twins are equally prone to the disorder. Furthermore, a difference in susceptibility or the absence of a difference, considered together with the various embryological implications, might throw light on the embryological background of mongolism.

Among white twins in New York State exclusive of New York City (1936–1937), *Yerushalmy* and *Sheerar* found 30 per cent to be of opposite sex. Unpublished data of *Firschein* provide a similar New York City figure for the years 1952 to 1954. Among mongoloid twins, however, the proportion of opposite-sex twins is presumably higher, because of an increased frequency of DZ twinning in maternal ages where mongolism is more common. Table 8 shows that 35 per cent of mongoloid twins should come from opposite-sex pairs. Of the 32 cases found in New York State Schools, 15, or 47 per cent, are from opposite-sex pairs. This discrepancy is not statistically significant ($t = 1.4$), but it cannot be ignored until a larger sample becomes available.

Table 8. Distribution of Mongoloids, Twins, and Mongoloid Twins by Maternal Age.

Maternal Age	Twin Births per 1000 Live Births[1]		Expected Distribution of 1000 Mongoloids[2]	Twin Births Expected Among the Same 1000 Mongoloids[3]		
	Same-sex	Opp.-sex		Same-sex	Opp.-sex	Total
Under 20	4.71	1.48	27	0.13	0.047	0.17
20–24	6.92	2.02	120	0.83	0.24	1.07
25–29	7.84	3.57	162	1.27	0.58	1.85
30–34	8.69	4.47	184	1.60	0.82	2.42
35–39	10.34	5.26	268	2.77	1.41	4.18
40 and over	6.67	5.56	239	1.59	1.33	2.92
All Ages	7.67	3.35	1000	8.19	4.42	12.61
All Twins	11.02			12.61		
Proportions of Twin Types	.696	.304		.6495	.3505	1.00

[1] *Yerushalmy* and *Sheerar*, 1940. [2] *Malzberg*, 1950.

[3] These figures show only relative incidence. They would correspond to absolute incidence if all mongoloid pairs were concordant.

The same-sex twins (table 8) are expected to comprise (8.19–4.42) 8.19, or 46 per cent MZ twins and 54 per cent DZ twins. Of the eight same-sex cases of known zygosity from State Schools, only two (one pair) were monozygotic, but if all four concordant pairs are tentatively considered monozygotic and all nine discordant pairs dizygotic, the proportions are almost exactly as expected. 47 per cent of the same-sex cases then come from MZ pairs. The excess of DZ twins shown in table 3 consists mainly or entirely of the opposite-sex pairs.

An incidental finding appears in table 9. Since the index cases are both twins and mongoloid, maternal ages are expected to be

Table 9. Observed and Expected Distribution of Maternal Ages in the Twin Sample.

Maternal Age at Birth of Twins	Number of Cases Observed	Expected Number	Expected Number if All Twins Were Dizygotic
Under 30	3	7.84	6.23
30–34	7	6.14	5.93
35–39	21	10.61	10.21
40 and over	1	7.41	9.63
Total	32	32.0	32.0
χ^2		18.82	19.98

high, and should follow the same distribution as all mongoloid twins in the last column of table 8. This distribution, applied to the number of twin mongoloids in State Schools, is given under "Expected Number" in table 9. It is seen to fit the observations very poorly with a χ^2 of 18.8, significant at the .01 level. Adjustment for a possible large excess of DZ twins in the sample does not account for the observed distribution of maternal ages. If all the twins were dizygotic, the maternal ages should be distributed as in the last column of the table, which gives a still larger value for χ^2. Allowance should, however, be made for the fact that all four concordant pairs were born to mothers in the age range from 35 to 39[1], so that the sampling error of this group corresponds to 17 rather than 21 independent observations. If χ^2 is calculated for the distribution of twin pairs instead of cases, the result is 13.7, still significant at the .01 level. Hence the high incidence in maternal ages 35–39, while unquestionably of some significance, does not lend weight to the slight excess of opposite-sex or DZ twins.

5. Concordance and Discordance

Table 3 summarizes the findings with respect to concordance for mongolism, omitting case 19 whose cotwin was not sufficiently observed. It has already been mentioned that 46 per cent of all same-sex twin pairs affected by mongolism should be monozygotic. This figure is very closely approached in the State School series if all concordant pairs are assumed to be monozygotic and all discordant pairs, dizygotic. So far as zygosity determination was possible, these two assumptions are born out, but cases 4 and 5 may well have been a concordant dizygotic pair. Data of this kind furnish useful upper limits for low concordance or discordance rates, which will be discussed later.

6. Normal Cotwins

With respect to the 27 living nonmongoloid twin or triplet partners of the mongoloids, special interest is attached to the possible effects of deleterious influences in early gestation. If responsible for mongolism in the index cases, such influences might be

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[1] It is interesting that the two other concordant pairs, who are not from State Schools, were born to mothers 38 and 45 years old.

expected to produce partial mongolism in the twin partners. Indeed, one might expect all the cotwins to be mongoloid. The numbers of cotwins and siblings were not large enough to warrant special study in comparison with the normal population, involving the difficult task of finding suitable control material. It should be possible, however, to recognize specific effects of the mongoloid pregnancy by comparing the cotwins with their own siblings.

Of the 18 families investigated, one provided no siblings. The others yielded a total of 41, whose age and sex distribution is shown in table 10 together with that of the 16 twin and 2 triplet partners. The ages refer to the date of examination. There were twice as many males as females among the cotwins, but the siblings were divided equally between the sexes. The median age of the sibs was four years and ten months higher than that of the cotwins (33 older and 8 younger sibs). As the numbers in the tables indicate, a few of the cotwins and siblings were not examined for all traits studied.

Table 10. Age and Sex Distribution of Cotwins and Siblings

Case No.	Cotwins		Siblings		
	Male	Female	Male	Female	Total
3	26		29	34, 39	3
8		13		9	1
10		12	25	13	2
13		8	13, 14	10	3
16	26		25, 42	23, 34, 34 37, 38	7
17		10	3, 11, 17		3
18	12		17, 18	7	3
20	15		10	13, 18, 19	4
22	2		7	10	2
23	14		12		1
24	8			16	1
25	11			21	1
26	16			22	1
27		8	11, 14	13, 23	4
30	11, 11		16		1
31	9		10, 13		2
34		2	11	3	2
Number	12	6	20	21	41
Median Age	11.4 years		16.3 years		

The findings will be discussed under the following headings: A. Intelligence; B. Mongoloid Features; C. Measurements; D. Dermatoglyphics.

A. *Intelligence:* The Stanford-Binet test was used in most cases to determine intelligence quotients, although some scores, provided by schools, were based upon group tests. For the institutionalized cases (mongoloids) the *Kuhlman-Binet* test was employed where the Stanford was not applicable.

The mean intelligence quotients are included in table 13, together with the physical measurements. The mean of the cotwins was 98.6 and of the siblings, 104.8. Neither value deviates significantly from 100, and the difference between the two groups is also insignificant, although the cotwins tend in the direction of mongolism. A more precise measure of the cotwin-sibling difference is obtained by comparing each cotwin with the mean of his siblings. If the difference in each family is weighted by the square root of the number of siblings (the number of comparisons on which the difference is based), and is averaged for all families, the mean cotwin-sibling difference with respect to intelligence is 6.7.

The intelligence of cotwins has a correlation with sibling means of $0.13 \pm .23$ in 15 comparisons. Correlation of the mongoloid intelligence quotients with the mean for all their siblings (14 comparisons) is .073. Both coefficients are far below the usual .5 correlation found among siblings, but are of course statistically inconclusive.

B. *Mongoloid Features:* Cotwins and siblings were examined for the following qualitative features, suggestive of mongolism: occipital flattening, nasal hypoplasia, internal epicanthus, fissured tongue, short hands, malformed fifth finger, palmar simian crease, separation of the first and second toes, and laxity of joints. These traits were scored from 0 to 3, with half-values for unilateral manifestation. Unit value was given to other anomalies, as listed in table 11, but subjects were not examined systematically for such defects.

The relative mongoloid tendencies of the index cases and their cotwins and siblings are shown in table 12, expressed as a mean score for each trait. The next-to-last column gives the sum of the cotwin-sibling differences, weighted except for the anomalies in the same way as intelligence. The traits with positive values in the next-to-last column occurred more often or more markedly in siblings

Table 11. Anomalies in the Mongoloid Sibships

Case No.	Mongoloid	Cotwin	Siblings
3	ptosis, syndactyly of toes	alopecia (subtotal)	
16	hallux valgus		
17	short 1^{st} metatarsal		Crooked 2^{nd} finger
18	ptosis, undescended testes		
20	symphalangy of toes, clubbing of nails		extreme brachycephaly
23	symphalangy of thumb, short 4^{th} metatarsals		
24	hypertelorism		
25	ichthyosis, deformed ears		
26	cardiac defect, ichthyosis		
30	hydrocephaly	rt ear lobe absent	
31	total alopecia (from age 5), strabismus	microcephaly, short hallux	
34	internal strabismus	peg teeth	
Number	19	5	2

than in cotwins, while traits with a negative sign predominated in the cotwins. The sums of the plus and minus scores differ by only 9.6, and in the direction that tends to discount mongoloid tendencies in cotwins beyond those shared by their siblings. This crude sum, however, neglects the fact that some traits may be more

Table 12. Mongoloid Features in Mongoloids and their Cotwins and Siblings.

Trait	Mean Score			Sum of Cotwin-Sib Differences	Ratio of Mean Scores, Mongoloids Over Siblings
	Mongoloids	Cotwins	Siblings		
Occipital Flattening	4.3	0.9	1.6	+ 21.9	2.6
Nasal Hypoplasia	4.3	0.4	0.4	— 3.0	9.7
Internal Epicanthus	2.1	1.0	0.6	— 10.7	3.2
Fissured Tongue	2.4	1.0	0.5	— 14.1	4.7
Short Hands	4.1	0.9	0.9	+ 0.3	4.8
Malformed 5^{th} Finger	2.7	0.0	0.4	+ 10.8	6.3
Simian Crease	2.4	0.0	0.2	+ 6.9	10.8
Separation of Toes 1,2	4.8	0.4	0.4	— 1.6	12.6
Laxity of Joints	4.7	0.9	1.3	— 0.7	3.8
Other Anomalies	1.2	0.3	0.0	— 0.2	24.3
Total	33.0	5.8	6.3	+ 9.6	5.2

significant than others, and assumes comparable scoring scales for all traits.

The relative significance of the traits is indicated by the ratio of mean score of the mongoloids to mean score of sibs. The cotwin-sib differences can be made comparable for all traits by dividing each by the respective mean sib score. When the cotwin-sib differences are standardized in this way and the results are weighted by the ratios in the last column of table 12, the total score for mongoloid tendencies again has a positive sign, confirming the original impression that the cotwins are not more mongoloid than their siblings.

C. *Measurements:* While the recognition and scaling of mongoloid features is susceptible to subjective error, physical measurements (table 13) are objective and relatively easy to evaluate. The measurements obtained were stature, ear height in the longest axis, head length, and head width.

The stature of each subject was compared by sex and by age to the nearest month with standard growth tables of the U.S. Department of Health, Education and Welfare [1953], supplemented in the preschool ages with data from a table assembled and used at Babies' Hospital in New York. The applicability of the growth curves used is indicated by the fact that the average deviation from expectancy in 41 siblings was only 0.18 per cent. This finding might be cited as evidence against any familial mon-

Table 13. Measurements of Mongoloids and their Cotwins and Siblings

Trait	Mongoloids n = 16*		Cotwins n = 18		Siblings n = 41		Standard Error (Difference)	Weighted Mean Cotwin-Sib Difference
	Mean	S.D.**	Mean	S.D.	Mean	S.D.		
Stature (Deviation from Standard in %)	—17.2	9.1	—0.7	4.7	+0.2	5.1	1.35	—0.91
Ear Height (Deviation from Standard in %)	—19.2	6.1	—0.5	4.9	+0.4	4.1	1.32	—0.68
Cephalic Index	84.5	2.4	78.7	3.6	79.7	4.3	1.07	+0.97
Head Size (Deviation from Standard in %)	—17.4	5.3	—2.6	6.6	—1.9	5.4	1.77	—2.44
Intelligence Quotient***	29.6	10.2	98.6	12.0	104.8	16.6	3.94	—6.65

* For cephalic index and head size the hydrocephalic patient was omitted, making n = 15.
** S.D. = Standard Deviation.
*** Numbers used were 14 mongoloids, 17 cotwins and 39 siblings.

goloid tendency with respect to stature. The cotwins fell below the standard by 0.7 per cent, and the weighted mean difference between cotwins and their own siblings was —0.91 per cent. The standard error of the difference as given in table 13 is based on the full numbers of cotwins and sibs. It is somewhat smaller than the correct value, which would be based on weighted family data with a smaller equivalent number of independent observations.

The constancy of subnormal ear size in mongoloids, which may have quantitative diagnostic usefulness, will be more fully discussed in a later report (*Ross* and *Allen*). Normative data on ear growth are hard to find, but it was necessary in the present analysis to make some correction for age. For this purpose use was made of our own normal subjects, supplemented in the younger age groups with white nonmongoloid new admissions to Willowbrook State School. The subjects were divided by age into seven nearly equal groups, and means and standard deviations were computed as shown in table 14. From these data a smoothed growth curve was obtained for estimating the expected ear height for each subject. The mean deviations from expectancy, —3.56 in females and +2.98 in males, were subtracted from the first-calculated deviations. Hence, ear measurements, like stature, were finally expressed in per cent deviation from standard for age and (approximately) for sex. By weighted mean difference, the cotwins' ears were found to be only 0.68 per cent smaller than those of the siblings.

Since the cotwins had smaller ears on the average and were generally younger than their siblings, their inclusion in the standard may have diminished the estimate of the cotwin-sibling difference. For the cotwins would tend to depress that part of the growth curve where they were most numerous and would have little effect on the

Table 14. Age Changes in Ear Height

Ages	Number of Subjects	Mean Age	Mean Ear Height in Millimeters	Standard Deviation	Cotwins (See Text)
1–2	10	1.93	49.2	2.3	2
3–6	10	4.44	53.9	4.0	0
7–9	8	8.32	58.2	3.8	4
10–11	10	10.99	60.7	3.8	4
12–13	11	13.02	61.6	3.9	3
14–19	11	16.98	62.4	3.3	3
20 and over	15	30.5	63.5	3.7	2

upper end of the growth curve, where siblings predominated. However, the last column of table 14 shows that cotwins occurred rather uniformly throughout the age range, so that this effect may safely be disregarded.

Head measurements were used in two ways. The cephalic index (width/length $\times$ 100) was taken as the best measure of head shape. Since age and sex differences in cephalic index are very small, comparisons were based upon uncorrected cephalic index rather than upon deviations from a standard. In this instance the siblings, rather than the cotwins, came closer to the mongoloids, as shown in the table, but the difference is smaller than its standard error.

In the second application of the head measurements, width and length were multiplied to give a measure of head size[1]. The products were expressed in square centimeters and compared with products of head measurements given for sex and age groups in standard tables. In this case tables of the U.S. Department of Health, Education and Welfare [1953] were supplemented in the earliest ages with data from *Martin* [1928]. Deviations were converted to per cent of standard. The mean deviation for sibs and cotwins was —2.1 per cent, S.E. 0.74, which may mean either that the standards came from a racially or culturally different population or that the families of mongoloids tend to have smaller heads than normal. The first interpretation seems more likely.

In terms of the weighted mean difference, the cotwins were 2.44 points below their siblings, but the standard error of the difference is at least 1.77. This difference comes closer to having significance than the other measurements, and its accuracy is made doubtful by the poor congruity of the total data and the standard. When the deviations are studied more closely, it appears that they have a positive correlation of .31 with age. In other words, the older subjects come closer to the standard than do the younger ones. Since the cotwins are younger, the faulty standard tends to exaggerate the negative deviation of the cotwins relative to that of the siblings. Hence a standard more appropriate to the sample would probable diminish, rather than increase, the significance of the cotwin-sibling difference.

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[1] Correlations were computed between cranial capacity and length-width products for the first 100 male and the first 100 female skulls listed by *Shapiro* [1929]. The coefficients were .749 $\pm$ .044 for males and .745 $\pm$ .044 for females, indicating that for certain purposes length-width products may be a useful measure of head size.

The same four measurements were used in comparing the eight younger with the 33 older siblings. The obtained differences are —2.6 for stature, —0.4 for ear height, +1.3 for cephalic index and —0.6 for head size. While these deviations are not significant, they are in the same direction as those of the cotwins. This observation suggests that the deviations of the cotwins are dependent upon age or order of birth rather than on the mongoloid pregnancy.

Table 15. Dermatoglyphics of Mongoloids and their Cotwins and Siblings

	Mongoloid Twins (30 hands)	Cotwins (36 hands)	Siblings (80 hands)	Normal Population	Mongoloid Population
	Frequency of Ulnar Loops on Each Finger, in Per Cent[1]				
Digit					
I	63.3	58.4	60.4	60.0	71.8
II	93.3	33.4	35.0	33.7	82.3
III	93.3	77.1	71.3	71.1	85.0
IV	70.0	55.6	56.3	56.1	59.4
V	76.6	77.8	82.5	84.7	76.2
χ^2 and Degrees of Freedom	29.1 (4)		.884 (5)		
	Termination of Palmar Main Line D, in Per Cent[2]				
Position					
7	11.1	27.6	24.3	11.7	4.2
8	2.8	4.3	5.6	3.9	0.0
9	11.1	21.3	25.2	32.4	12.1
10	16.7	17.0	19.6	13.1	2.9
11	58.4	29.8	25.2	38.7	77.0
13	0.0	0.0	0.0	0.0	4.6
χ^2 and Degrees of Freedom	7.93 (3)		.651 (4)		
	Frequency of patterns in each palmar area[2]				
Area					
Hypothenar	66.7	38.9	37.5	37.2	58.2
Thenar / I	3.3	5.6	12.5	5.5	1.6
II	3.3	5.6	2.5	4.2	5.4
III	83.3	50.0	51.2	40.8	95.5
IV	33.3	66.7	68.8	49.0	19.4
χ^2 and Degrees of Freedom	17.4 (3)		.390 (4)		

[1] Population data from *Dr. Norma Ford Walker*, unpublished.
[2] Population data from *Snedecker*, 1948.

To summarize the metrical findings, the cotwins of mongoloids differed from their siblings in the direction of mongolism with respect to stature, ear height, and head size, and in the opposite direction with respect to head shape. However, the observed differences were statistically insignificant and very small in comparison with the deviations seen in the mongoloid index cases. Since the later-born siblings deviated in the same direction, it can be said that objective measurements of the cotwins failed to show any specific effects of the mongoloid pregnancy.

D. *Dermatoglyphics:* Statistical differences between mongoloids and nonmongoloids with respect to skin ridge patterns are well established (*Cummins* [1939]). These should provide a rather sensitive measure of mongoloid tendency in a series like the present one[1]. Dermatoglyphics have the great advantages of being completely objective and practically uninfluenced by sex, age or health.

Comparisons between cotwins and sibs (and mongoloids) were confined to four dermatoglyphic traits: (a) the frequency of ulnar loops on each finger in per cent; (b) the point of termination of the palmar main line D; (c) the frequency with which any pattern occurred in each of the palmar areas; and (d) the frequency of the distal triradius, t″, in the palm. Data on the first three characters are given in table 15 together with comparative statistics of other investigators. The same data are presented graphically in figure 4. At all points where mongoloids are expected to differ significantly

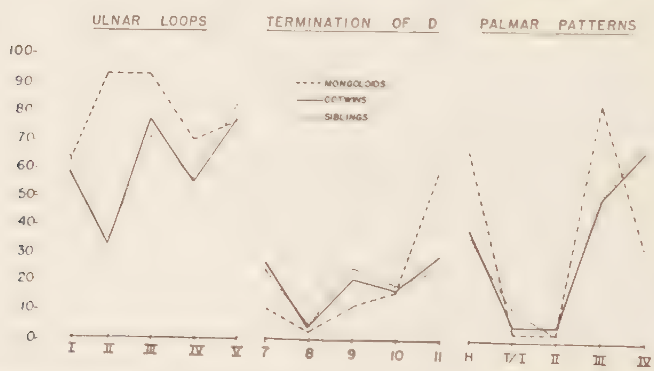

Fig. 4. Dermatoglyphic comparison of mongoloids, their cotwins and their siblings.

[1] Grateful acknowledgment is here made to Dr. *Norma Ford Walker* for the dermatoglyphic analysis of Case 18 and his partner, as well as for technical assistance at the time this study was undertaken.

from normal, the cotwins adhere closely to the frequencies of their normal siblings. The low values of χ^2 obtained for the differences between cotwins and siblings, shown in the table, indicate a resemblance that is significant at the five per cent level. This is to be expected, since each cotwin is more closely related to one or more of the siblings than to any of the other cotwins. In contrast, the differences between mongoloids and their cotwins are all significantly large, two of them at the one per cent confidence level.

The presence of a distal triradius in the palm is recognized by the angle subtended at the palmar triradius by the triradii *a* and *d*, which must be greater than 57° (*Penrose* [1954b]). This feature was seen in one or both hands in 80 per cent of the mongoloids and in 16.7 per cent of the cotwins, but in only 5 per cent of the siblings. At first glance, this finding might be interpreted as a mongoloid trend in the cotwins. However, a percentage of 16.7 is close to *Penrose*'s figure of 15 per cent for all siblings of mongoloids. Of chief interest, therefore, is the low rate for our group of sibs, which falls below *Penrose*'s figure by three times its standard error. This difference may actually not be statistically significant because many of the subjects are genetically related and this fact is not expressed in the standard error.

The difference between cotwins and siblings in frequency of the palmar triradius t″ does not reach the level of statistical significance, but is compatible with the view that the palmar dermatoglyphics may be influenced by the embryonic environment.

7. Discussion

Statistical twin data on mongolism are usually based on collected case reports. A consecutive series of mongoloid twins can be used in two ways: first, as an independent check on the conclusions obtained from collected reports, and, second, to enlarge the number of these cases, thereby extending the statistical conclusions.

In order for the basic data to have the full validity of unselected material, there is need, first, for assurance of nearly complete ascertainment of cases in the cooperating institutions. The possibility of significant bias from this source was discussed in section 4. The observed trend was toward underrepresentation of discordant and especially of opposite-sex twins, but the present data do not show a significant deviation in this respect. Second, one would like to

know in what ways the institutional and the general population of mongoloid twins differ from each other. It is conceivable, for example, that concordant pairs, being more burdensome to their families, are institutionalized more regularly than are discordant pairs. This tendency would result in an excess of MZ twins, but no such excess has been found in the present series. Finally, the population from which index cases are drawn should be describable in statistical terms. This consideration restricts useful analysis of the mongoloid cases to 32 institutionalized patients.

The data presented in table 6 and section 4 show no evidence of a different frequency of twins among mongoloids than among normal children born at the same maternal ages. Even at the upper limit of the 95 per cent confidence interval, the true frequency of twins corresponding to these data would be only 1.3 times the frequency calculated for mongoloids. This finding may have etiological implications, since twinning results from abnormal processes in the mother or in the zygote and exercises abnormal influences over at least the later stages of gestation. If any major factor were common to both mongolism and twinning, or if either condition tended to cause or to preclude the other, a definite discrepancy in twin frequencies would be expected.

Even maternal age, which is positively related to both mongolism and the two types of twinning (*Krooth* [1955]), may be assumed to operate by separate mechanisms in these conditions. One reason for this conclusion is the absence of any apparent interaction between twinning and mongolism. The present data show a lesser degree of association between these conditions than would be expected even from their known separate associations with maternal age. Another reason is that, although maternal age has a stronger influence on dizygotic than on monozygotic twinning, the presence of mongolism in this series of twins has not significantly altered the ratio of zygosity types. Of course, a larger series of twins would add weight to this argument. Finally, dizygotic twin births increase uniformly to maternal age 35–39 and thereafter remain stable (*Yerushalmy* and *Sheerar* [1940]) or decline (*McArthur* [1954]). In contrast, the association of mongolism with maternal age begins at about 27 years and progresses geometrically to the end of the reproductive period (*Penrose* [1954 a]).

Two observations in this study, however, may indicate a subtle etiological connection between twinning and mongolism. The first

is the large but statistically insignificant excess of opposite-sex pairs among the dizygotic twins. The other is the significant excess of twins born in the maternal age range 35–39, where dizygotic twinning is at a maximum. The excess of opposite-sex pairs cannot be disregarded because, although there is no evidence for such an excess in the literature, the frequency of opposite-sex pairs is likely to be underestimated except under complete ascertainment (see table 7). In this connection it should be noted that sex in itself has little if any effect on the expression of mongolism. The most extreme sex ratio cited, that for newborn mongoloids by *Hug* [1951], gives 65 per cent males, and this figure is contradicted by the data of *Øster* [1953]. The observed excess of twins born in the maternal age range 35–39 may represent some special bias due, for example, to institutionalization. It was most marked among the concordant pairs; among six such pairs, five were born to mothers in this age period, the remaining pair being one of two that were not in a State School.

Much attention has been given to the question of partial mongolism and to the occurrence of stigmata of mongolism in otherwise normal persons among close relatives of mongoloids (*Doxiades* and *Portius* [1938], *Penrose* [1954b]). If such subclinical manifestations were a result of intrauterine influences, they would be most strongly expressed in the twin partners of mongoloid patients, while if they depended upon genetic factors they would be equally expressed in cotwins and siblings. In this study the cotwins of mongoloids showed no statistically significant mongoloid tendencies in comparison with their own siblings. The most suggestive differences were in intelligence, head size, and frequency of the distal palmar triradius. The first difference might represent the depression of intelligence test scores reported for twins in general (*Zazzo* [1952], *Lorimer* [1952]). The second might be attributed partly to the fact that one of the cotwins had clinical microcephaly (head circumference 48.3 cm. at age 9, I.Q. 70) without other physical stigmata of mongolism. The frequency of the distal palmar triradius in the cotwins is high only by comparison with an abnormally low frequency in their siblings.

The frequency with which dizygotic cotwins of mongoloids may be affected is not known. No concordant pair on record has been proved to be dizygotic by a difference in sex or in blood antigens. Of four pairs usually cited as dizygotic, only one can be accepted

with assurance (*McKaye* [1936]). In a pair described by *Russel* [1933], the zygosity diagnosis was based on the assumption that only dizygotic twins may have two fetal envelopes. The pair reported by *Gordon* and *Roberts* [1938] was atypical. The pair reported by *Jervis* [1943] is included in the present sample. Although the patients have died, a reexamination of the fingerprints casts some doubt on their dizygotic status.

In the present study, the 21 pairs from State Schools who were proved to be dizygotic were all discordant. This sets an upper limit for the concordance rate in DZ twins in terms of the likelihood that such a sample should contain no concordant pair. The upper limit thus obtained is 14 per cent concordance if the sample has a probability of at least five per cent. If 14 per cent of the DZ twins belong to concordant pairs, the concordance rate (*Allen* [1955]) in DZ twins would be:

$$\frac{14/2}{14/2 + 86} = .075$$

If the doubtful cases 4 and 5 are accepted as a DZ pair, the frequency becomes 2/23 and the concordance rate is 4.5 per cent.

The best evidence comes from opposite-sex pairs, whose dizygotic status is beyond question. There seems to be no objection to adding the 42 opposite-sex pairs from the literature (*Friedman* [1955]) to the 15 in this study, since it may be assumed that mongolism occurring in both partners of an opposite-sex pair is at least as likely to be reported as mongolism occurring in one member of such a pair. In all of these 57 opposite-sex pairs the partner has been found to be normal. At the five per cent confidence level it can therefore be said that not more than 5.2 per cent of all opposite-sex twins represent concordant pairs, and the corresponding figure for concordance is 2.7 per cent of twin pairs. There is no apparent reason to doubt the validity of this figure for DZ twins of same sex also; the present data show that mongolism occurs at least as often in opposite-sex as in same-sex twins.

Concordance is an expression of morbidity expectancy. Therefore, 14 per cent is the upper limit of morbidity expectancy in dizygotic cotwins of mongoloids. If the collected reports of opposite-sex pairs can be relied upon, the limit drops to 5.2 per cent. Even the second figure is higher than the frequency of sibships containing two mongoloids (*Jervis* [1943]), but this is not the crucial compari-

son. According to *Böök* and *Reed* [1950], the morbidity expectancy of siblings born after a mongoloid is 3.9 per cent (95 per cent confidence limits 1.4 and 8.4). This represents a 20-fold increase of expectancy over that for pregnancies not preceded by the birth of a mongoloid. It appears that the morbidity of dizygotic cotwins born *with* mongoloids is very similar to that of siblings born *after* mongoloids. If so, the responsible maternal factor in mongolism appears to be some slight but permanent and very specific impairment of reproductive functions.

At the time of the latest review (*Friedman* [1955]), no evidence had been presented for the occurrence of one-egg twins of whom one was mongoloid and the other normal. An alleged instance has now been described by *van Beukering* and *Vervoorn* [1956]. In this case, however, monozygosity was diagnosed only from a specimen of placental septum, which was found to contain no chorion. Taken by itself, this evidence cannot be regarded as establishing an exception to the general rule; one case is on record of opposite-sex twins separated at birth by no membranes at all (*Pickering* [1946]).

In our institutional series of 21 discordant pairs, blood typing or homograft evidence for dizygosity was obtained in all but one pair, and that pair was clearly dissimilar in hair color and in two of three dermatoglyphic characters. From this fact one can conclude at the five per cent probability level that not more than 14 per cent of discordant mongoloid pairs are monozygotic. If we add the 65 discordant pairs collected from the literature and considered dizygotic by *Friedman* [1955] and the questionable MZ pair of van *van Beukering* and *Vervoorn*, the proportion drops to 1.2 per cent with an upper limit of 6.3.

The expected proportion of MZ pairs among mongoloid twins is 30 per cent if one accepts the present evidence for equal susceptibility of the two types of twins. This gives a ratio of MZ to DZ twins of 3 to 7, or .43, while the highest ratio among discordant pairs that is compatible with the collected data is .067. The proportion of discordant pairs is at least six times as great in DZ twins as in MZ twins. In fact, available data do not preclude the possibility that MZ twins are never discordant.

The high concordance rate of monozygotic twins with respect to mongolism supports one or both of the following etiological explanations: (1) The maternal influence acts decisively on the developing ovum or on a very early stage of the embryo, in a spo-

radic manner (involving, perhaps, a threshold which is rarely passed). (2) A pathological response to the abnormal intrauterine environment is determined by the genotype of the embryo at whatever stage the environment exerts its effect.

The first explanation is the now classic theory of the defective ovum (*Jenkins* [1933]). The second is the widely applicable concept of genetically conditioned susceptibility to a noxious influence, first applied to mongolism by *Tredgold* [1908]. This author identified the genetic factors with a general "neuropathic" constitution, but he later abandoned the theory. That the susceptibility may have a biochemical basis has been suggested in an anonymous article in the British Medical Journal (1954).

The occurrence of mongolism in a baby born to a mongoloid mother (*Lelong* et al. [1949]) supports the hypothesis that susceptibility in the fetus and the responsible influence in the mother have a common genetic basis, but other hypotheses might also explain the observation. No abnormality of the child was recorded in five other instances of childbearing by mongoloids mentioned in the literature (*Lind* [1923], *Rosenberg* [1924, two births], *Brousseau* [1928] and *Sawyer* [1949]).

Penrose has found evidence [1951, 1954b] that the maternal pathology associated with mongolism has some dependence on maternal heredity. At least one dermatoglyphic trait of mongoloids, the distal palmar triradius, is demonstrable in a significantly high proportion of the presumed genetic carriers (mothers and siblings). This abortive expression of mongolism suggests some embryonic vulnerability shared by the mothers of mongoloids and some of their offspring. Apparently the genetically susceptible earlier-born siblings of a mongoloid develop normally only because they are not challenged by an adverse maternal environment. Even after the establishment of an adverse environment as evidenced by the birth of a mongoloid, most embryos (or ova) are resistant and develop normally. This appears to be equally true of twin partners conceived at the same time as a mongoloid.

Since a young mother seems to be capable of compensating the defect of a susceptible ovum or embryo, *Penrose*'s findings offer hope that medical science may discover a specific biochemical defect common to mongoloids and their mothers. Pharmacological compensation for such a defect before conception would prevent mongolism.

8. *Conclusions*

According to the findings of the present study, there is no major etiological connection between mongolism and twinning. Evidence obtained from twins on the nature and causation of mongolism should therefore apply to mongoloids in general.

Comparison of dizygotic cotwins of mongoloids with their own siblings shows that if temporary intrauterine conditions produce mongolism in the index case, they do not bring about any changes in the cotwin that can be regarded as partial mongolism. This observation confirms the prevalent view of mongolism as a disorder of development that follows *en bloc* from some early accident of development, with variations that rarely confuse the main pathological picture.

The consecutive series of twin mongoloids here described bears out the main conclusions derived by other authors from collected case reports. Not more than 14 per cent of twin pairs discordant for mongolism are monozygotic, and it is even likely that monozygotic pairs are never discordant. It therefore appears that susceptibility to mongolism is predetermined at the very start of development in either the cytoplasm or the genes of the embryo.

Not more than 5.2 per cent of mongoloids with opposite-sex twin partners represent concordant pairs, and the maximum concordance rate is 2.7 per cent. These figures probably hold for dizygotic twins in general and they agree well with the expectancy of mongolism reported for siblings born after a mongoloid.

The similarity of morbidity rates in mongoloids' dizygotic twin partners and in their subsequent siblings suggests that the risk, once established, remains approximately uniform or may increase. The maternal factor in the etiology of mongolism is therefore to be sought in a more or less permanent change that has occurred in the physiology of the mother's reproductive or endocrine system, and not in some event or transient state associated with the mongoloid pregnancy. However, only about five per cent of embryos may be vulnerable in this environment.

Summary

A statewide study of mentally defective twins brought to light 39 cases of mongolism in twins, 32 of whom came from the definable population of the New York State schools for mental defectives.

In addition to 15 opposite-sex pairs, 11 same-sex pairs could be classified by zygosity. Three of the same-sex pairs were found to be monozygotic and concordant, while all of 23 dizygotic pairs were discordant. The classification of one concordant pair as dizygotic by another investigator could not be confirmed with current dermatoglyphic methods.

Altogether, 18 nonmongoloid cotwins and 41 normal siblings were used for studies of intelligence and physical stigmata of mongolism. Neither group showed a significant mongoloid trend with respect to intelligence or stature, the only traits for which reliable normative data are available. For all traits studied, the cotwins and their siblings proved to be similar within the limits of sampling error.

A review of the present series together with all cases of mongoloid twins in the literature indicates that the morbidity expectancy in monozygotic cotwins of mongoloids is close to 100 per cent. The corresponding rate for dizygotic cotwins does not seem to exceed that of their later-born siblings, approximately four per cent.

It is concluded that the etiology of mongolism is to be sought not in a transient noxious influence during the mongoloid pregnancy, but in some more or less permanent change in the mother's reproductive or endocrine system. In order to produce a mongoloid child, this maternal influence apparently has to act upon a genetically predisposed embryo, or upon the ovum, or upon the embryo prior to the earliest stage when twinning occurs by division.

Résumé

Lors d'un examen de jumeaux avec débilité mentale, fait dans l'Etat de New-York, on a trouvé parmi ceux-ci 39 cas de mongolisme. 15 de ces couples étaient de sexe différent. Chez 11 couples d'un même sexe, on a pu faire le diagnostic du type de gémellité – 3 couples étaient univitellins et concordants, tandis que tous les 23 couples bivitellins étaient discordants. 18 couples non-mongoliques et 41 frères et sœurs normaux ont été examinés au point de vue de l'intelligence et des signes somatiques du mongolisme. Dans aucun de ces cas on n'a pu constater de trait certain de mongolisme.

Basé sur le présent examen et sur tous les cas de mongolisme chez des jumeaux publiés antérieurement, le risque de maladie du

partenaire d'un jumeau univitellin mongolique peut être calculé à 100% à peu près; pour le partenaire d'un jumeau bivitellin mongolique, ce chiffre n'est que de 4%, c'est-à-dire pas plus élevé que pour les frères et sœurs puînés. On en conclut donc que la cause du mongolisme ne doit pas être recherchée dans une influence nocive passagère durant la grossesse, mais dans une altération plus ou moins permanente du système reproductif et endocrinien de la mère.

Zusammenfassung

Eine Untersuchung schwachsinniger Zwillinge im Staat New York ergab 39 Fälle von Mongolismus bei Zwillingen, von denen 32 unter den Insassen der Schulen des Staates New York für schwachsinnige Kinder gefunden wurden. Außer bei 15 Zwillingspaaren verschiedenen Geschlechts konnte noch bei 11 gleichgeschlechtlichen Paaren die Eiigkeitsdiagnose gestellt werden. Drei der gleichgeschlechtlichen Paare erwiesen sich als monozygotisch und konkordant, während alle 23 dizygotischen Paare diskordant waren. Insgesamt wurden 18 nicht-mongoloide Paarlinge und 41 normale Geschwister für die Studien von Intelligenz und psychischen Zeichen von Mongolismus benutzt. Diese Gruppen zeigten keine sicher auf Mongolismus hinweisenden Anomalien in bezug auf Intelligenz und Statur. Alle untersuchten Züge der Paarlinge und ihrer Geschwister erwiesen sich als gleich innerhalb der Grenzen von Auswahlfehlern.

Eine Durchsicht der vorliegenden Reihen und aller Fälle von Mongolismus bei Zwillingen in dem diesbezüglichen Schrifttum zeigt, daß die Krankheitserwartung bei monozygotischen Paarlingen mongoloider Zwillinge fast 100% ausmacht. Der entsprechende Prozentsatz für dizygotische Paarlinge scheint nicht den ihrer später geborenen Geschwister, etwa 4%, zu übersteigen.

Es wird hieraus die Schlußfolgerung gezogen, daß die Ätiologie des Mongolismus nicht auf einen flüchtigen schädlichen Einfluß während der mongoloiden Schwangerschaft zurückzuführen ist, sondern von einer mehr oder weniger ständigen Änderung in dem Fortpflanzungs- oder endokrinen System der Mutter herrührt. Um ein mongoloides Kind zu erzeugen, muß dieser mütterliche Einfluß offenbar auf einen prädisponierten Embryo oder auf das Ei oder auf den Embryo während des frühesten Stadiums, ehe die Zwillingsbildung durch Teilung stattfindet, einwirken.

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GENETICAL INVESTIGATIONS IN A NORTH-SWEDISH POPULATION MANDIBULO-FACIAL DYSOSTOSIS

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Introduction

For several years, the genetic morbidity and the population genetics of three parishes in North-Sweden have been studied (*Böök* [1948, 1953 and 1956]). For a detailed description of this population, which constitutes a so-called geographical isolate, the reader is referred to the above-mentioned papers. At the population survey of 1949, one family with mandibulo-facial dysostosis was registered. This family has now been followed up and examined more closely. As mandibulo-facial dysostosis is a very rare disorder, and as the present family may contribute to the knowledge of intra-familial variations, a report seems justified.

Definition and Previous Literature

Mandibulo-facial dysostosis is a genetic condition with the following main diagnostic features: "Anti-mongoloid" temporal slope of the palpebral fissures, coloboma of the lateral part of the lower lids, hypoplasia of the zygomatic processes, malar bones and mandible, malformation of the external and sometimes also the middle and inner ear, macrostomia, irregular teeth and malocclusion, blind fistulae between the angles of the mouth and the ears, tongue shaped processes of the hair line towards the cheeks. Occasionally other anomalies may be found. This syndrome was first reported by *Thomson* in 1846–47 (cf. *Klein* [1953]) and defined as a distinct clinical entity by *Franceschetti* and *Zwahlen* in 1944.

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Franceschetti and *Klein* [1949] have published a monograph in which the clinical and genetic features of mandibulo-facial dysostosis, as well as the previous literature, are discussed in detail. Some Dutch cases and a comprehensive discussion of the pathogenesis were published by *Waardenburg* and *Navis* [1949]. Recently *Vannus* [1955] reported two Finnish cases with unilateral mandibulo-facial dysostosis.

The clinical signs of this condition show many variations. A number of incomplete or abortive cases have been reported. For a discussion of the relation between mandibulo-facial dysostosis and allied conditions the reader is referred to *Goldenhar* [1952], who also listed all cases published since 1949. The papers of *Streiff* [1950] and *Franceschetti* and *Klein* [1954] contain additional information on mandibulo-facial dysostosis and related malformations. In the English literature, this condition is sometimes called the Treacher-Collin syndrome.

Most authors seem to agree that mandibulo-facial dysostosis is primarily due to a single autosomal gene difference manifesting itself in heterozygotes. However, the variability in expression is sometimes considerable. In some families, the mode of inheritance has been interpreted as "irregular dominance".

Case reports

The pedigree of the present family has been outlined in fig. 1. In his first marriage, the father (VII:1) had two children without signs of mandibulo-facial dysostosis; VIII:2 was mentally deficient. In his second marriage, which was with the sister of his first wife, three normal and three malformed children were born.

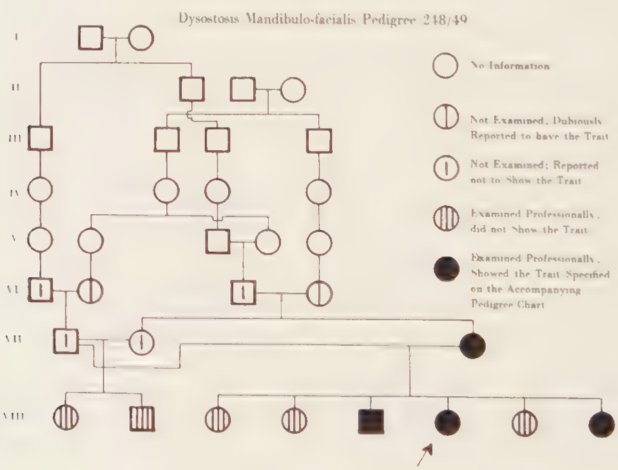

Fig. 1

According to information given by VII:3 in the pedigree, VI:2 as well as VI:4 had laterally sloping palpebral fissures but no other obvious peculiarities. Their hearing and eyesight was normal. Slightly expressed "anti-mongoloid" eyes could be seen on amateur photographs. The possibility that a mild form of mandibulo-facial dysostosis was present must be taken into account.

VII:1. Born in 1905. Refused examination. Insofar as could be judged by a causal inspection, he displayed no signs typical of mandibulo-facial dysostosis. Unfortunately, these negative observations are not conclusive and the possibility that some slight deviation exists must be taken into account.

VII:2. Female, born in 1912; died in 1941 of pulmonary tuberculosis. Reported as normal. No signs of mandibulo-facial dysostosis could be seen on amateur photographs.

VII:3. Female, born in 1914. Menarche at 15 years of age. Married in 1944. She had six completed pregnancies and no abortions. She had had German measles as a child and erythema nodosum in 1946. Repeated controls at a TB-clinic showed no signs of pulmonary or other forms of tuberculosis. All pregnancies were uneventful and deliveries normal.

Examined in 1956 (*Böök*): Athletic body type. Both palpebral fissures displayed a clear "anti-mongoloid" slant. At palpation, both malar and zygomatic processes appeared smaller than normal. She had a retracting, comparatively small mandible (cf. fig. 2). She had macrostomia, but otherwise the oral cavity displayed no abnormalities. All teeth had been removed. External ears and auditory canals were normal. No other skeletal deformities were found. Internal organs, eyes and the nervous system showed normal conditions on routine physical examination.

Diagnosis: Dysostosis mandibulo-facialis, moderate form.

VIII:5. Male, born April 28, 1949; died May 21, 1949. Normal delivery. Examined May 13, 1949 at Gällivare Hospital, division of pediatrics. He was very thin and atrophic. He had no external ears and the auditory canals were obliterated. The eyes were small and the eyelids could be opened only to a narrow slit. He also had a cleft palate. Weight: 2,180 g.

Diagnosis: Dysostosis mandibulo-facialis + palatoschisis.

VIII:6. Female, born in 1950. Normal delivery, but the mother had hydramnion at the end of the pregnancy. Birth weight: 4.050 g. Examined at the pediatric division, Boden Hospital, April 2, 1951. She had a birdlike appearance with a small face, caput quadratum, hypoplastic mandible and "anti-mongoloid" eyes. Both auricles were represented only by small and malformed skin lobes and no auditory canals could be seen. Her head circumference was 41.5 cm. The large fontanel was 25×25 cm and felt normal. She was rather thin and showed slight signs of rickets. The oral cavity appeared normal. A physical examination of the internal organs disclosed no pathological changes. An examination of sound perception was inconclusive. Laboratory data (April 3, 1951): Hemoglobin 71 per cent, red cells 3.6 million per cu. mm., white cells 7,400 per cu. mm., color index 1.01; differential count: 20.5 per cent stab cells, 1 per cent eosinophils, 72 per cent lymphocytes, 6.5 per cent monocytes. The red cells displayed slight anisocytosis. Sept. 27, 1952: Hemoglobin 68 per cent, red cells 3.7 millions per cu. mm., white

Fig. 2. Mandibulo-facial dysostosis in mother and daughter (nos. VII: 3 and VIII: 6 of the pedigree in fig. 1).

cells 6,200 per cu. mm., color index 0.99. Differential count: stab cells 27 per cent, eosinophils 7 per cent, lymphocytes 61 per cent, monocytes 2 per cent, basophils 3 per cent. The red cells displayed typical anisocytosis. Slight granulocytopenia.

At the age of 1 year she had measles. She could sit at 6 months and walked at 11 months. At a new examination in Sept. 1952, she could say only a few words. Sound perception appeared normal. A neurological examination showed normal conditions.

X-ray examination of the skull showed a normal labyrinth, cochlea and cavum tympani in the temporal bones. Her *Wassermann* reaction of the blood was negative. Toxoplasmosis was excluded, the dye test according to *Sabin*-

Feldman was negative at a serum dilution of 1:10, and the complement fixation test with toxoplasma antigen was negative at a serum dilution of 1:7.5 (Oct. 1952).

In June, 1953, she was taken to the hospital in Gällivare because of diarrhea and vomiting. She recovered after a few days. Her weight was 12 kg. Her *Mantoux* reaction was negative.

Examined in 1955 (*Böök*): She was very shy and cried most of the time. According to the mother, she was able to hear if shouted to. Her mental development was apparently slightly retarded. She could say only a few words.

Her general physical condition was fair. As mentioned above, she displayed several signs typical of mandibular facial dysostosis (cf. fig. 2), i.e.

1. "anti-mongoloid" obliqueness of the palpebral fissures;
2. colobomas of outer part of the lower lids;
3. hypoplasia of the squamous part of the malar and zygomatic process of the temporal bones;
4. hypoplasia of the mandible;
5. bilateral malformation of the external ears;
6. bilateral obliteration of the auditory canals;
7. macrostomia;
8. irregular, crowded teeth but no hypodontia.

The oral cavity was otherwise normal. A routine physical examination of internal organs and the nervous system showed normal conditions.

Diagnosis: Dysostosis mandibulo-facialis.

VIII:8. Female, born June 23, 1953; died August 26, 1953. Her birth weight was 3,650 g. She was very weak, had a grey, pale skin and stridorous breathing. She was cared for at the local hospital and was never taken home. Her insufficient circulation was interpreted as being due to a congenital malformation of the heart. The external ears were malformed and the auditory canals were lacking. She had a cleft palate, a large hemangioma of the left cheek and another hemangioma below the tongue. At the age of 7 weeks, she became increasingly cyanotic, got severe diarrhea and died.

Diagnosis: Dysostosis mandibulo-facialis + palatoschisis.

Comments

The proposita of this family displayed typical signs of mandibulo-facial dysostosis. The observation of a moderate anemia and granulocytopenia on two occasions is worth noticing. Connections between defects of bone development and bone marrow function are known in other conditions, e.g. hemolytic icterus. A further exploration of such a mechanism in mandibulo-facial dysostosis is suggested, especially with regard to severe forms.

The two sibs affected with a severe, lethal or semi-lethal, form

of mandibulo-facial dysostosis resulting in death at the age of one and two months agree with the observations of *Franceschetti* and *Klein* [1949] that in many instances the gene has a sublethal effect. *Debusman* [1940 cf. op. l.c.] reported a family in which 3 sibs out of 6 displayed the complete syndrome and died within the first six months of life.

The number of individuals with mandibulo-facial dysostosis who die by reproductive age should be quite considerable. One major cause of death could be congenital malformations of the heart. Such malformations were probably present in one of our cases and has been reported by *Roussell* [1951] and *Gottsegen* [1956].

No attempts have as yet been made to determine the general morbid risk of mandibulo-facial dysostosis. No doubt the condition is rare. *Goldenhar* [1952] collected 39 published reports with a total of 84 cases. On the other hand, interest has been focused on this condition only recently. Furthermore, considering that mild forms may pass unnoticed, the gene itself may not be too uncommon in the general population.

The present pedigree deserves some comments. The simplest explanation is that a gene in heterozygous condition is responsible for all affected members. Then the consanguinity of the parents is a coincidence compatible with the high frequency of inbreeding in this population (cf. *Böök* [1956]). The severe forms could be due to the effect of some other rare pathological gene in double dose. This may be true for the congenital haemangiomata observed in VIII:8, but probably not for the cleft palate of VIII:8 and VIII:5. Cleft palate is quite a common feature of the syndrome (*Franceschetti* and *Klein* [1949]).

Another explanation is that the father also had the gene with a weak manifestation. In such a case, the severely affected sibs might have been homozygotes.

Summary

A consanguineous North-Swedish family with mandibulo-facial dysostosis is described. The mother and three children out of six were affected. Two children were severely affected and died at the age of one and two months, respectively. The penetrance and expressivity of this genetic syndrome are briefly discussed.

Résumé

Il s'agit d'une famille consanguine du Nord de la Suède affectée de dysostose mandibulo-faciale. La mère et 3 enfants sur 6 étaient atteints. 2 des enfants étaient gravement atteints et moururent à l'âge respectif de 1 et 2 mois. La pénétrance et l'expression de ce syndrome génétique est exposé en résumé.

Zusammenfassung

Eine nord-schwedische Familie mit Dysostosis mandibulo-facialis wird beschrieben. Die Mutter und drei von sechs Kindern waren affiziert. Zwei Kinder hatten schwere Mißbildungen und starben im Alter von ein und zwei Monaten. Die Penetranz und Expressivität dieses genetischen Syndroms wird kurz besprochen.

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THE CALCULATION OF MORBID RISK IN PARENTS OF INDEX CASES, AS APPLIED TO A FAMILY SAMPLE OF SCHIZOPHRENICS

By ERIK ESSEN-MÖLLER

1.

The families of 73 index cases or probands suffering from schizophrenic psychosis were investigated. Out of the known 143 parents (70 fathers and 73 mothers) of these probands, 5 were manifestly schizophrenic, which gives a crude incidence of 3.5 per cent.

The vast majority of parents had at observation already passed the full risk period for schizophrenia, and those remaining were as a rule fairly close to the upper limit of that period. With *Strömgren*'s tables of accumulated percentual risks at different years of age, the total of 143 observations so far correspond to 141.86 full risk periods (Table I), so that the corrected morbid risk still remains 3.5 per cent. The finding is in accordance with those reported in literature, where the risk in question is usually given as 3–5 per cent (*Schulz*, *Kallmann*).

By way of contrast, the risk in children of schizophrenic probands is usually reported to be 8–16 per cent. According to *Mendel*ian rules, and independently of the mode of inheritance, the same risk should be valid for parents and children alike. The most plausible explanation of this discrepancy is the considerable reduction of reproductivity known to be present in schizophrenics and resulting in a reduced number of schizophrenic parents (*Essen-Möller*, *Koller*). In fact, *Böök*'s exceptional finding of a risk in

parents as high as 12 per cent is combined with that of a comparatively small reduction of reproductivity in his probands.

Closer scrutiny reveals that the method of computation itself, as presented above, is not free from bias. According to this method, parents and children of probands are both regarded as though observed from birth until age at investigation (or death), and as though exposed to risk already from the beginning of the risk period. However, parents of probands do not really enter into observation until precisely the moment of birth *of the proband*, and the computation should therefore be confined to what happens later. Thus admittedly a man aged 40 has passed .96 of his full risk period, but in case he has not entered the observation until he was 35 (if this was his age at birth of the proband), as much as .88 of a full risk period was already over before his entering, and this man should by rights contribute only .08 to a full observation.

From this consideration, the age of all parents at birth of the respective probands was registered, and, with the aid of *Strömgren*'s tables, the risk periods really under observation were marked off. In fact, the majority of risks are now considerably reduced, the sum of them amounting to 11.82 full periods only in fathers, 25.59 in mothers, and 37.41 (instead of 141.86) in all parents taken together (Table I).

As for the 5 parents with a schizophrenia, 4 manifested their disease later than the birth of the respective proband. In relation to the total of risks observed, this means a morbid risk of 4/37.41 = 10.8 (instead of 3.5) per cent. It also means that the discrepancy between risk of parents and risk of children appears to have been eliminated.

Originally, when trying this method of calculation, I hesitated whether or not to include in the numerator also the fifth of the schizophrenic parents, who manifested his disease already before the birth of his proband child. However, as demonstrated to me by my friend Professor *Quensel* of the Statistical Institute of this University, such inclusion would involve also a correction of the denominator according to a general approach to the problem. This idea may be formulated as follows.

2.

Since the starting-point of the investigation is taken in probands, the group of parents may be conceived of as belonging to a hypo-

Table I

Number of parents N	Age attained: at investigation[1] y	Age attained: at birth of proband x	Covered fraction of risk: at investigation I_y	Covered fraction of risk: at birth of proband I_x	Covered fraction of risk: during observation $I_y - I_x$
Mothers:					
1		21	1.	.19	.81
1	51	21	.98	.19	.79
1		22	1.	.24	.76
1	56	22	.99	.24	.75
1		23	1.	.28	.72
2		24	1.	.33	.67
4		25	1.	.38	.62
1	55	25	.99	.38	.61
1		26	1.	.42	.58
1	55	26	.99	.42	.57
1	43	26	.90	.42	.48
3		27	1.	.47	.53
1	44	27	.92	.47	.45
1		28	1.	.51	.49
1		29	1.	.55	.45
1	56	29	.99	.55	.44
1	48	29	.96	.55	.41
3		30	1.	.59	.41
1	52	30	.98	.59	.39
5		31	1.	.62	.38
3		32	1.	.66	.34
2		33	1.	.69	.31
1	52	33	.98	.69	.29
1		34	1.	.72	.28
4		35	1.	.75	.25
7		36	1.	.77	.23
6		37	1.	.79	.21
3		38	1.	.82	.18
3		39	1.	.84	.16
1	52	39	.98	.84	.14
3		40	1.	.85	.15
2		41	1.	.87	.13
1		42	1.	.89	.11
1		43	1.	.90	.10
1		45	1.	.93	.07
2		46	1.	.94	.06
73			72.66	47.07	25.59

(continued)

Table I (continued)

Number of parents N	Age attained		Covered fraction of risk		
	at investigation[1] y	at birth of proband x	at investigation I_y	at birth of proband I_x	during observation $I_y - I_x$
Fathers:					
1	25	22	.47	.29	.18
2		23	1.	.35	.65
2		24	1.	.41	.59
3		26	1.	.53	.47
3		27	1.	.59	.41
1	30	27	.73	.59	.14
2		28	1.	.64	.36
5		29	1.	.69	.31
2		30	1.	.73	.27
5		31	1.	.77	.23
3		32	1.	.81	.19
3		33	1.	.84	.16
2		34	1.	.86	.14
2		36	1.	.91	.09
5		37	1.	.92	.08
4		39	1.	.95	.05
1		40	1.	.96	.04
3		41	1.	.97	.03
5		42–43	1.	.98	.02
8		44–46	1.	.99	.01
8		> 46	1.	1.00	.00
70			69.20	57.38	11.82
Fathers and mothers:					
143			141.86	104.45	37.41

[1] In case the age at investigation is beyond the risk period (more than 56 years in women and more than 46 years in men), it is omitted from the table.

thetic matrix population of individuals so equipped, from a genetic point of view, that each of them would produce a proband as soon as becoming father or mother (environmental factors disregarded). However, not all of them will actually become parents, and only those who do so will be subject to our investigation. Therefore the material investigated is no random sample of the hypothetic population but a selection according to parenthood.

At age $x, y, \ldots$, let the morbid risk already passed up to that time be denoted by $I_x P$, $I_y P, \ldots$. Here P is the maximum risk connected with a full risk period, and I_x, $I_y, \ldots$ are the accumulated fractions of this risk already passed at the respective age. Thus P is the risk ultimately to be ascertained, and I_x, I_y are the partial risks accounted for, in the case of schizophrenia, in the aforementioned tables of *Strömgren*, and ranging from 0 to 1. Then $P(I_y - I_x)$ will make up the risk pertaining to the span of age between x and y (y being higher than x). It is generally assumed that the series of accumulated risk fractions, as obtained originally from probands, is valid also for parents and is independent of the level of P.

At age x, the hypothetic *matrix population* may be divided into three parts:

(1) individuals diseased prior to that age, with a relative frequency of PI_x;

(2) individuals who will manifest the disease later, frequency $P - PI_x$; and

(3) individuals who will never get the disease, frequency $1 - P$.

The sum of frequencies is $= 1$.

Out of these individuals, a certain proportion only will be parents and thus be included in an investigation beginning with probands. Here the proportion of those who become parents at the age of x will be denoted, within the three groups, as g_{1x}, g_{2x}, and g_{3x} respectively. By way of simplification, we may assume that their mutual relations remain constant throughout all ages, and we may also put $g_{3x} = 1$. The three weights are then written as g_1, g_2, and 1.

The three groups who become *parents* at age x will then occur with the following frequencies (in relation to the total hypothetic matrix population):

manifestly affected	$g_1 PI_x$;
later to be manifest	$g_2(P - PI_x)$; and
never to be manifest	$1 \cdot (1 - P)$.

The total frequency of parents aged x is therefore

$$g_1 PI_x + g_2(P - PI_x) + 1 \cdot (1 - P) \tag{A}$$

The frequency of *diseased parents* at age x is, accordingly, $= g_1 PI_x$. At age y, two groups of diseased parents may be distinguished, namely, those having been manifestly ill as early as at age x, and

those having become so between ages x and y. The total frequency of diseased parents at age y is then

$$g_1 P I_x + g_2 P(I_y - I_x) \tag{B}$$

Let now y denote the age at leaving the observation or the age at investigation. Then (B) is the relative frequency, within the hypothetic population, of such diseased parents as became parents at age x and who were later observed at age y, while (A) is the frequency of parents who ever entered the material. Bringing these frequencies into relation to each other, we get

$$\frac{g_1 P I_x + g_2 P(I_y - I_x)}{g_1 P I_x + g_2 P(1 - I_x) + 1 \cdot (1-P)} \tag{C}$$

as an expression of the *probability* that any one parent investigated will be found to be manifestly affected.

The *average* of these individual probabilities will be equal to the observed frequency in the parents $\left(\frac{n}{N}\right)$, which enables us to compute the value of P. The average itself may be obtained (since the denominator does not much deviate from 1) as the quotient of the sum of the numerators by the sum of the denominators, $\Sigma\,(C) = appr.\ \frac{\Sigma\,(B)}{\Sigma\,(A)}$

Therefore, and since $\sum^{N} 1 = N$,

$$\frac{g_1 P \Sigma I_x + g_2 P \Sigma (I_y - I_x)}{g_1 P \Sigma I_x + g_2 P N - g_2 P \Sigma I_x + N - PN} = \frac{n}{N}\,; \tag{D}$$

and, finally, the *morbid risk* is obtained as

$$P = \frac{n}{g_1 \Sigma I_x + g_2 \Sigma (I_y - I_x) + n\left[1 - g_2 + (g_2 - g_1)\,\frac{\Sigma I_x}{N}\right]} \tag{E}$$

It will be noted that the use of formula (E) does not require that the parent's age at manifestation is known. This surely is an advantage, since at investigation it will often be difficult to ascertain this age with accuracy.

3.

As a first application of the formula (E), let us suppose that the reproductivity is identical within the three groups ($g_1 = g_2 = g_3 = 1$). The formula is then reduced to

$$P = \frac{n}{\Sigma I_y}, \qquad \text{(F)}$$

which corresponds to the way of calculating hitherto commonly used, in putting the number of diseased parents into relation with the total risks passed until the time of investigation. Accordingly, the use of this method should be confined to the case of reproductivity being uninfluenced by the disease.

Again, if reproductivity remains uninfluenced until manifestation of the disease and then ceases ($g_1 = 0$; $g_2 = g_3 = 1$), the formula (E) turns into

$$P = \frac{n}{\Sigma\,(I_y - I_x) + \frac{n}{N}\,\Sigma\, I_x}, \text{ or, approximately, } P = \frac{n}{\Sigma\,(I_y - I_x)}, \qquad \text{(G)}$$

which is obviously the way of calculating introduced in the first section of this paper. It will be seen that the numerator n cannot, in this case, contain any parents with an onset of disease prior to the births of probands.

On intermediate assumptions as to reproductivity, the complete formula (E) comes into play. For instance, we may estimate the average reproductivity in Schizophrenics as approximately $1/3$ of that of the surrounding population and specify this average as $g_2 = 4/9$ before and $g_1 = 2/9$ after manifestation. (These assumptions are borne out by findings made by the present author in the two cited papers.) We then get

$$\frac{5}{0.22 \cdot 104.45 + 0.44 \cdot 37.41 + 5 \left| 1 - 0.44 + (0.44\text{–}0.22)\,\frac{104.45}{143} \right|} = 11.6\,\%$$

This is about the same risk as was computed in the first section, that is, by the aid of formula (G), but, of course, the material is more thoroughly utilized here because account is taken also of part of early risks and manifestations.

In other populations, different rates of reproductivity and perhaps also different distributions of risks may occur. The age at

birth of probands will, however, remain essentially within the risk period of schizophrenia, and any deviation in reproductivity will therefore continue to influence the computation in regard to this psychosis. In a disease like *Huntington*'s chorea, with its risk period located to a greater extent to ages higher than those during which most parents have their children, the interplay of the relevant factors is again a different one.

Summary

The current method of computing the morbid risk for a given disease in parents of probands (or index cases) may sometimes lead to inadequate results, namely as soon as the disease is involved with a change in reproductivity. An improved method is therefore suggested (formula E). As before, knowledge is required of the relative distribution of accumulated risks according to age. In addition, one has to know the relative change in reproductivity in affected persons prior to and following the manifestation of the disease, as well as the age of parents at birth of the probands.

As regards schizophrenia, the risk in parents of probands usually given as 3–5 per cent, by this method of calculation rises to about 11 per cent for the present material. The inequality of risks hitherto noted in parents and children, in itself a somewhat striking feature from a *Mendel*ian point of view, seems hereby to have been eliminated.

Résumé

La façon habituelle d'évaluer les risques de maladies chez les parents des probands peut parfois donner des résultats trompeurs, du moins dès que la maladie en question est associée à un changement de la reproductivité. C'est pourquoi l'on propose une amélioration de la méthode de calcul (formule E). Cela suppose que, de même que jusqu'à présent, l'on connaisse la grandeur relative du risque accru de maladie, à différents âges, et, en outre, il est indispensable de connaître le changement de la reproductivité avant et après la maladie, ainsi que l'âge des parents à la naissance des probands.

En ce qui concerne la schizophrénie, cette méthode donne un risque de maladie plus élevé que les 3-5% généralement obtenus jusqu'ici, à savoir 11% dans le cas présent. Ceci fait également

ressortir que cette différence concernant les risques de maladie entre parents et enfants de probands, insatisfaisante du point de vue mendélien, semble être éliminée.

Zusammenfassung

Die übliche Berechnungsweise der Krankheitserwartung unter Probandeneltern ist unter Umständen irreführend, und zwar sobald die betreffende Krankheit mit einer Abänderung der Reproduktivität, d.h. der Häufigkeit des Elternwerdens, verknüpft ist. Eine verbesserte Methode der Berechnung wird deshalb vorgeschlagen (Formel E). Diese erfordert, wie auch die bisherige Methode, Kenntnis der relativen Verteilung des Erkrankungsrisikos je nach verschiedenen Altersstufen, und außerdem die Kenntnis der relativen Veränderung der Reproduktivität vor und nach Beginn der Krankheit sowie des Alters der Eltern bei Geburt der Probanden.

Für die Schizophrenie ergibt sich durch diese Technik eine höhere Krankheitserwartung als die üblich angenommene von 3-5%, und zwar im vorliegenden Material etwa 11%. Die bisherige, vom *Mendel*schen Gesichtspunkt aus auffallende Diskrepanz der Krankheitserwartung zwischen Eltern und Kindern von Probanden scheint damit beseitigt zu sein.

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EXAMEN ANATOMO-CLINIQUE D'UN CAS D'IDIOTIE AMAUROTIQUE INFANTILE (TAY-SACHS)

Par A. FRANCESCHETTI, E. WILDI et D. KLEIN

Depuis la mise en évidence de la nouvelle entité clinique, l'idiotie amaurotique infantile, par *Tay* [1881] et *Sachs* [1887], l'intérêt porté à cette curieuse et cruelle maladie a toujours été très vif, comme le prouve l'abondante littérature estimée aujourd'hui à 260 cas environ. Considérée tout d'abord comme un processus d'ordre purement nerveux dû, selon *Sachs*, à un arrêt du développement cérébral ou, selon *Schaffer*, à une hérédo-dégénérescence (abiotrophie), les recherches histo-pathologiques et biochimiques ultérieures ont montré qu'il fallait plutôt la classer dans le groupe des thésaurismoses lipidiques, à côté des maladies de *Niemann-Pick* et de *Gaucher* et des xanthomatoses.

La symptomatologie clinique de la maladie de *Tay-Sachs* présente en général un aspect assez uniforme: l'affection débute au cours des six premiers mois de la vie et se caractérise par la triade: régression psychique, amaurose (avec l'image ophtalmoscopique classique de la tache rouge cerise de la macula) et troubles moteurs (hypertonie, spasmes toniques et cloniques, paralysie progressive). La maladie aboutit à la mort, le plus souvent entre la deuxième et la troisième année de la vie.

La dégénérescence «utriculaire», qui est le critère anatomopathologique de l'idiotie amaurotique infantile, fut mise en relief par *Schaffer* [1905]: altérations caractéristiques et ubiquitaires des

cellules ganglionnaires aussi bien au niveau du système nerveux central que sur toute l'étendue de la rétine. Les cellules, d'aspect ballonné, contiennent, dans la zone protoplasmique, de fines granulations lipidiques et des vacuoles.

L'image histo-pathologique, semblable dans les autres formes de l'idiotie amaurotique (formes juvénile, infantile tardive, adulte) bien que présentant certaines différences au point de vue extension et répartition du processus morbide, a permis de les grouper dans le même cadre nosologique comme différentes variétés cliniques d'un même trouble fondamental.

Tay [1884] et *Sachs* [1896], déjà, ont relevé le caractère hérédo-familial de l'affection. Il ressort du taux de consanguinité très élevé observé dans les familles atteintes (27,6% pour les cas publiés de 1884 à 1933, d'après *Slome;* 24,5% pour les cas de 1934 à 1954, d'après *Klein* et *Ktenidès*), ainsi que de la fréquence des enfants atteints (resp. 18,4% ± 2,7 et 22,2 ± 2,8; selon les auteurs précités), que l'affection suit en général un mode récessif d'hérédité.

Grâce à l'amabilité du Professeur *F. Bamatter* qui nous avait adressé un enfant provenant d'une famille valaisanne autochtone et atteint de maladie de *Tay-Sachs* (cas publié par *Bamatter* et *Sierro* [1949], et vérifié anatomiquement par *Wildi* [1950]), nous avons eu une fois déjà l'occasion d'examiner un cas typique au point de vue oculaire, génétique et anatomo-pathologique (*Ktenidès* [1954]).

Un nouveau cas de maladie de *Tay-Sachs*, d'origine libano-syrienne chrétienne, nous a donné l'occasion de reprendre ce sujet. Tandis que, cliniquement, l'observation différait peu de celles déjà publiées, l'enregistrement simultané de l'électroencéphalogramme et de l'électrorétinogramme nous a permis de faire certaines constatations intéressantes dont nous avons fait état dans notre rapport sur les lipidoses (*Franceschetti*, *Klein* et *Babel* [1955]).

La petite malade ayant succombé à sa grave maladie à l'âge de 28 mois, il nous a été possible, grâce à l'obligeance du Dr *R. Martin-du-Pan*, Genève, de procéder à une autopsie. La confrontation des données cliniques avec les documents histo-pathologiques du système nerveux et de la rétine justifie la présente publication.

Résumé clinique

Ho., Nicole, née le 7. 12. 1952, décédée le 5. 4. 1955 (Pol. N° 7912/53).

Anamnèse familiale (fig. 1). Parents chrétiens, non consanguins. Père d'origine libanaise, mère syrienne. Les deux sœurs et un frère aînés de la malade en bonne santé.

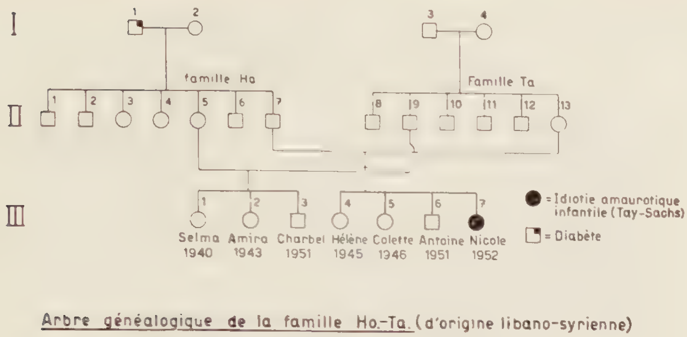

Fig. 1. Arbre généalogique de la famille Ho.-Ta.

Anamnèse personnelle. Enfant née à terme avec un poids de kg 3,700. Son développement se poursuivit normalement jusqu'à l'âge de six à sept mois. A cette époque, les parents commencèrent à s'inquiéter de la diminution de sa vivacité et de la faiblesse des jambes. L'enfant montrait en outre une hypersensibilité marquée au bruit. La petite malade nous fut envoyée par le Professeur *Sobhy*, du Caire, avec le diagnostic de maladie de *Tay-Sachs*.

Examen ophtalmologique (Clinique ophtalmologique, le 16. 10. 1953). Fillette de 10 mois dont l'état général est bon. Réaction des pupilles à la lumière un peu lente. Motilité oculaire normale. Fond d'œil: papilles bien délimitées, très pâles. Au niveau de la région maculaire, des deux côtés, on constate une zone gris blanc irrégulière avec une tache rouge foncé dans le centre fovéolaire, signe typique de la maladie de *Tay-Sachs*.

Status général (Dr *R. Martin-du-Pan*, Genève). On note une hypotonie musculaire généralisée, une incapacité de s'asseoir ou de se tenir assise seule (fig. 2 et 3), des réflexes tendineux faibles aux membres inférieurs, vifs aux membres supérieurs. La radiographie révèle un crâne en tour. L'examen psycho-moteur met en évidence un gros déficit psychique.

L'*électroencéphalogramme* (Dr *Monnier*, Genève) montre que l'activité électrique des régions postérieures du cerveau (pariéto-occipitales et temporo-occipitales) est anormalement faible. Les rythmes lents 4–7 c/s qui, chez l'enfant normal de cet âge, prédominent dans la région occipitale sont ici trop peu abondants. Il existe cependant un rythme 6 c/s assez bien systématisé dans les régions pariétales, surtout à droite, et antéposé, ainsi qu'on l'observe habituellement dans les retards du développement cérébral. Les épreuves de stimulation lumineuse confirment la non-réceptivité des appareils thalamo-occipitaux. L'éclairement ne provoque pas d'action nette sur les activités électriques du cerveau.

Un examen EEG pratiqué à la Clinique pédiatrique de Zurich (Prof. *G. Fanconi*) conclut à une dysrythmie généralisée et à une asymétrie aux dépens de la région occipitale droite; la photo-stimulation provoque des potentiels rappelant ceux de l'épilepsie (forme généralisée ou multifocale ?).

Electrorétinogramme (Dr *Dieterle*) enregistré au moyen de l'électroencéphalographe en utilisant comme électrode le verre de contact de *Henkes;* les réponses ont

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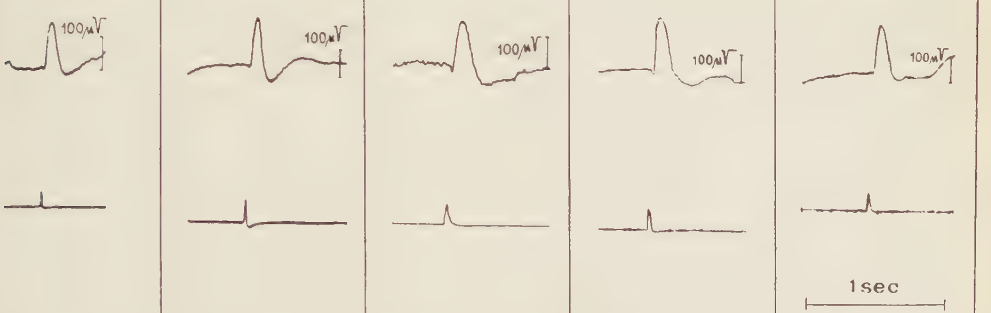
Fig. 2. Ho., Nicole, 1952 (1 an), maladie de *Tay-Sachs*. Hypotonie généralisée. L'enfant est incapable de se tenir assise seule et de lever la tête. – *Fig. 3.* Soutenue sous le dos, l'enfant montre une légère hypertonie des membres inférieurs.

été obtenues par une stimulation lumineuse stroboscopique. La figure 4 montre 5 tracés électrorétinographiques échelonnés entre l'âge de 11 et 28 mois. (L'onde b a été mesurée entre le point culminant de l'onde a et le sommet de l'onde b.) L'ERG se révèle normal dans les trois premiers tracés, c'est-à-dire jusqu'à l'âge de 19 mois, bien que présentant déjà une tendance supranormale. Les tracés IV et V, dont le dernier a été pris 7 jours avant la mort, indiquent une réponse électrique supranormale nette de la rétine. On peut en conclure que la fonction du neuroépithélium est intacte et que l'augmentation du potentiel d'action de la rétine doit être imputée à une atrophie du nerf optique. Cette lésion des fibres optiques, responsable de l'amaurose, est probablement en relation avec une atteinte des voies optiques ou des centres visuels mêmes. Cette conclusion se voit corroborée par le résultat de l'électroencéphalographie, qui indique une hypofonction de la région postérieure du cerveau.



Examen: 2. 11. 1953 (11 mois)	Examen: 11. 3. 1954 (15 mois)	Examen: 14. 7. 1954 (19 mois)	Examen: 21. 11. 1954 (23 ½ mois)	Examen: 29. 3. 1955 (28 mois)
Onde a: absente Onde b: +120 μV	Onde a: ± Onde b: +180 μV	Onde a: −15 μV Onde b: +180 μV	Onde a: −15 μV Onde b: +200 μV	Onde a: ± Onde b: +200 μV
ERG: à la limite inf. de la normale	ERG: à la limite sup. de la normale	ERG: à la limite sup. de la normale	ERG: supranormal	ERG: supranormal
I	II	III	IV	V

ig. *1.* Différents stades de l'enregistrement électrorétinographique dans notre cas de maladie de *Tay-Sachs.* (1 = ERG œil droit. 2 = Stim. lum.)

Evolution. A 11 mois et demi, l'enfant fut transférée à la Clinique infantile de Zurich (Professeur *G. Fanconi*) où les constatations suivantes furent faites: légère hypertonie musculaire, hypersensibilité excessive avec tressaillement à la moindre excitation extérieure, réflexes de *Moro* négatifs; les réflexes tendineux sont très vifs, avec des zones hyperréflexogènes; *Babinski* négatif, *Rossolimo* positif, *Gordon* et *Oppenheimer* négatifs, *Bechterew* positif, *Chvostek* négatif.

Le 3 février 1954, l'enfant est ramenée à Genève. On note une régression nette dans le tableau neurologique: hypertonie manifeste des membres, mais encore hypotonie du tronc (fig. 3); réflexe de défense plantaire à gauche net, avec *Babinski*, positif; à droite, aucun réflexe de défense plantaire, *Babinski* négatif; réflexe de préhension faible.

L'enfant décédait le 5.4.1955, donc à l'âge de 28 mois, et l'autopsie fut pratiquée le jour même.

Anatomie pathologique du système nerveux central (Dr *E. Wildi*) (fig. 5–11).

Examen macroscopique. Le cerveau pèse à l'état frais 1160 g. Sa forme globuleuse et hyperbrachycéphalique est due à un fort élargissement des deux lobes

Fig. 5. Section frontale avec écorce orbitaire et nerf optique. On remarque l'implantation du tractus olfactif au niveau de l'aire parolfactive. Démyélinisation naso-supérieure du nerf optique à 2 mm. en avant du chiasma. Méthode de *Weigert.*

pariétaux; à la face interne des hémisphères cérébraux, le lobule paracentral et le précunéus notamment offrent une surface nettement exagérée. Le cunéus est insuffisamment développé. Il existe une brièveté relative des lobes frontaux et occipitaux; ces derniers apparaissent même un peu en retrait sous la partie postérieure des lobes pariétaux.

A la surface des circonvolutions, les artères et les veines cheminent selon un tracé assez rectiligne, comme si les tortuosités vasculaires, normales à cet âge, avaient été effacées, consécutivement à un élargissement des circonvolutions.

A la face interne des hémisphères cérébraux, le corps calleux est un peu mince, court, arrondi autour des noyaux de la base. La commissure antérieure est hypoplasique; la commissure interthalamique, absente. Les deux trous de *Monro* sont faiblement dilatés, l'aqueduc l'est à peine. Il n'existe pas d'élargissement notable des ventricules latéraux. L'hypothalamus est attiré vers le bas et en avant. Les nerfs optiques sont trop minces, atrophiés, et apparaissent profondément démyélinisés dans leur cadran supéro-interne (fig. 5).

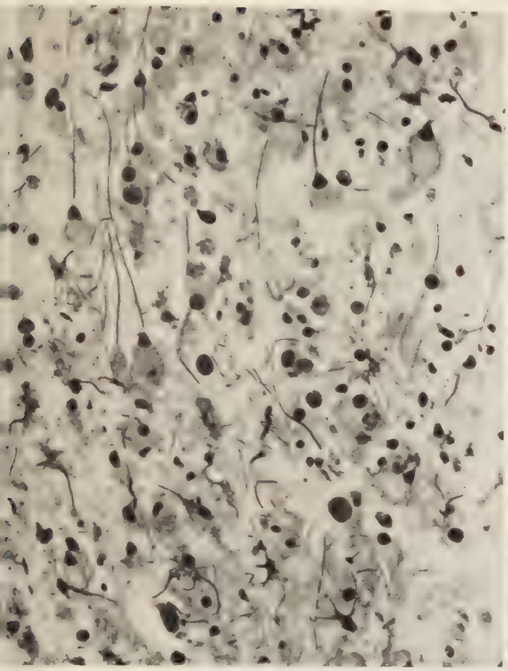
Des deux côtés, le sillon opto-strié sépare la tête trop volumineuse du noyau caudé de la masse thalamique, atrophiée, dont la consistance est ligneuse.

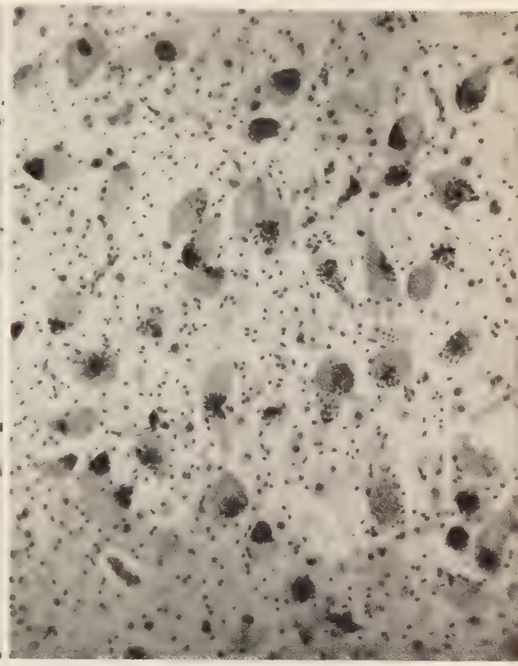
A l'inverse des circonvolutions hémisphériques, toutes trop larges, les lamelles de l'écorce cérébelleuse sont toutes trop étroites, sauf celles des amygdales, dont l'épaisseur est en moyenne le double de la leur. La consistance du cervelet est très ferme.

Les deux faisceaux pyramidaux sont diffusément démyélinisés.

La substance blanche sous-corticale, notamment celle de la partie distale des axes blancs, est presque partout un peu spongieuse.

Examen microscopique. Aucun neurone n'est totalement épargné par le processus d'entassement lipidique intracytoplasmique, aussi bien dans l'écorce cérébrale et cérébelleuse que dans les noyaux de la base du cerveau, le tronc cérébral et la moelle cervicale. Il n'y a guère qu'au niveau de la 3e couche isocorticale que subsistent quelques neurones non tigrolytiques, faiblement hyperchromiques et ratatinés. Le volume cellulaire est en général considérablement augmenté par l'entassement des lipides dont l'histochimie sera précisée plus bas (fig. 6).





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ig. 6. Pôle frontal, écorce cérébrale. Imprégnation argentique selon *Globus*. 153,6 ×. Ballonisation des eurones. Les noyaux cellulaires sont repoussés à l'émergence du dendrite apical qui n'est nulle part uméfié. Gliose fibrillaire. Présence de nombreux corps granulo-graisseux, de forme arrondie, présentant le l'affinité à la fois pour les sels d'argent et le soudan III. - *Fig. 7.* Locus niger. *Nissl.* 90 ×. Ballonisation les neurones: les corps tigrés sont repoussés contre le noyau cellulaire. Prolifération des noyaux gliaux.

Dans la couche des cellules de *Purkinje* et dans celle des petites cellules pyramidales de l'écorce (couche III), l'entassement pénètre jusque dans les dendrites. Dans tous les autres neurones, il reste circonscrit dans le voisinage du noyau cellulaire.

Dans la majorité des cellules, la substance tigroïde est quasi inexistante, réduite à une poussière très fine qui entoure le noyau. Ce n'est guère que dans certaines formations de la base du cerveau, de la moelle et du tronc cérébral qu'elle est bien conservée, malgré l'entassement lipidique. C'est ainsi que les corps tigrés subsistent avec une certaine massivité dans les cellules nigériennes (fig. 7), les motoneurones des nerfs crâniens et rachidiens.

Dans l'écorce cérébrale, les astrocytes montrent une augmentation telle de leur masse protoplasmique qu'ils arrivent pour la plupart à être plus volumineux que les neurones les plus gros. Ils sont souvent plurinucléés et présentent en de nombreux points des aspects monstrueux. Aux colorations habituelles, leur volume et la pâleur de leur noyau les font confondre avec les neurones du voisinage; ce n'est que grâce aux qualités histochimiques de leur contenu que leur identification est réalisable (voir tableau 1).

Dans la substance blanche, il y a en général moins d'astrocytes de ce type. La gliose s'y manifeste par un feutrage de fibrilles très fines et assez faiblement impré-

Fig. 8. Substance blanche préfrontale. Phosphatase acide selon *Gomori*. 153,6×. Surcharge phosphatasique dans les astrocytes et les cellules microgliales. Présence de quelques noyaux nus d'oligodendrogliocytes.

gnables par les sels d'argent. Toutefois, dans la substance blanche cérébelleuse, les astrocytes sont volumineux, d'aspect mi-protoplasmique, mi-fibrillaire, parfois binucléés.

Comme c'est la règle dans cette affection, la microglie réagit par une mobilisation et un entassement de lipides beaucoup plus soudanophiles que ceux contenus dans les neurones et les astrocytes. Les altérations microgliales prédominent fortement dans les couches profondes de l'écorce cérébrale (par exemple dans la couche IV de l'écorce frontale).

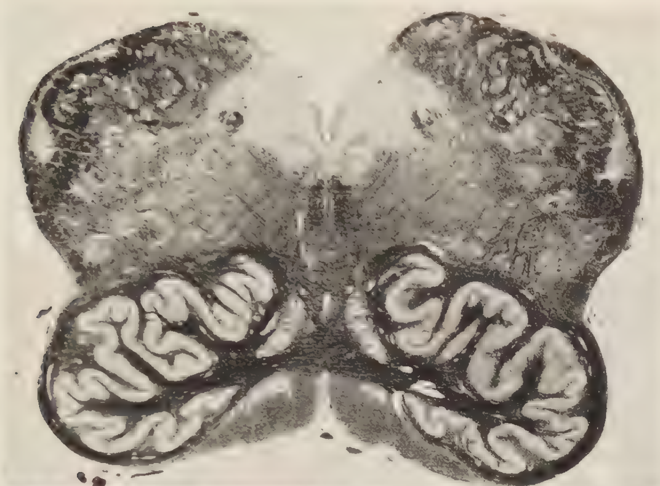
L'oligodendroglie ne prolifère pas; au contraire, elle semble raréfiée dans la substance blanche. Les préparations à la phosphatase acide, selon *Gomori*, mettent en évidence, dans la substance blanche sous-corticale, quelques noyaux nus d'oligodendrogliocytes, à côté d'astrocytes et de microgliocytes gorgés de ce ferment (fig. 8).

Le degré de maturation myélinique est insuffisant partout. Seul le corps calleux paraît à peu près normalement myélinisé, quoique un peu mince. Le défaut myélinique se voit surtout à la partie distale des axes blancs de toutes les circonvolutions et notamment aux pôles temporaux. Nulle part il ne subsiste trace de la couche des fibres en U de *Weigert*. La capsule blanche interne est assez profondément éclaircie. Les faisceaux pyramidaux sont très atrophiés devant les olives bulbaires et au niveau de leur décussation (fig. 9).

Les résultats obtenus par la recherche histochimique sont rassemblés dans le tableau 1.

Tableau 1

Coloration	Neurones		Microglie		Astroglie	
	congélation	paraffine	congélation	paraffine	congélation	paraffine
Soudan III . . .	(+)		+++		++	
Soudan noir B . .	+	(+)	+++	++	+	(+)
Bleu Alcian . . .	++	0	+++	+	++	0
PAS	++	0	+++	++	+	+
Perdreau		+		++		(+)
Mallory		0		bleue		bleue
Millon		0		0		0



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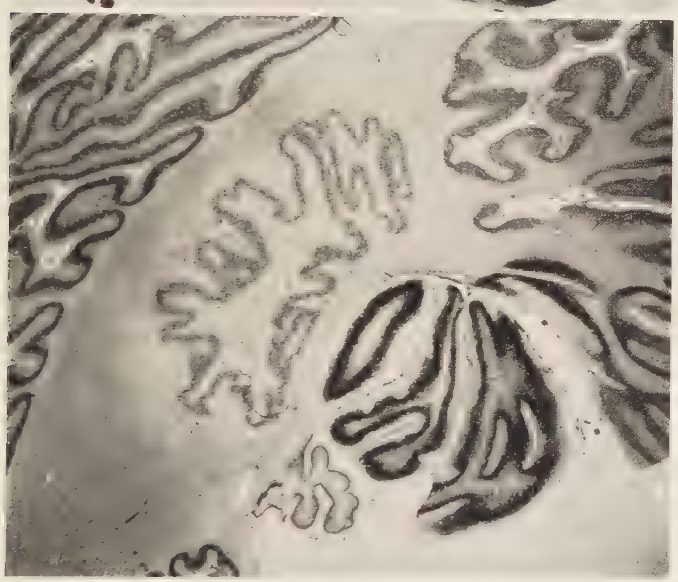

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Fig. 9. Bulbe rachidien. *Schroeder.* Faible grossissement. Atrophie et démyélinisation assez avancée des deux faisceaux pyramidaux. Massivité des olives, due en partie à l'entassement lipidique de leurs neurones. – *Fig. 10.* Cervelet. *Nissl.* Faible grossissement. Atrophie corticale profonde avec état discret de spongiose (multiples petites cavités). L'amygdale est la formation la moins atrophiée.

La détermination qualitative de la phosphatase acide, selon *Gomori*, non encore pratiquée à notre connaissance dans cette affection, a donné des résultats intéressants. Dans l'écorce, tous les neurones, les astrocytes et les cellules microgliales sont bourrés

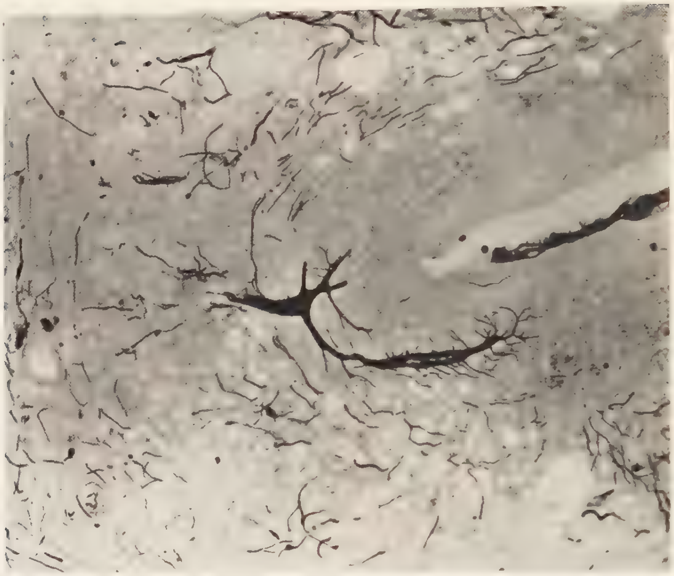

Fig. 11. Ecorce cérébelleuse. *Bielschowsky.* 165,6 ×. Gigantisme et aspect monstrueux des prolongements dendritiques d'une cellule de *Purkinje.* Noter l'aspect chevelu du dendrite.

de cette enzyme à un point tel que tout le contenu cellulaire semble n'être que de la phosphatase (fig. 8).

Devant le bulbe rachidien, l'artère basilaire est porteuse d'un minuscule épaississement fibreux sous-intimal du type artériosclérotique, avec dédoublement de la lame élastique interne.

Dans les leptoméninges se voient, en d'assez nombreux points, de minuscules artérioles présentant des parois faiblement épaissies, hyalines. La même altération artériolaire se retrouve aussi, quoique plus rarement, à l'intérieur du tronc cérébral.

A l'intérieur de l'écorce cérébrale, les noyaux des cellules endothéliales des capillaires et des artérioles sont tuméfiés, rendant le réseau vasculaire plus visible que dans une écorce normale. Dans les couches superficielles de l'écorce pré- et post-rolandique, il existe une argentaffinité nette de toutes les fines ramifications précapillaires. Dans certains petits foyers bien circonscrits, cette réticulose peut atteindre l'intensité de celle qu'on découvre dans les foyers de nécrose parenchymateuse sur base vasculaire.

Il faut faire une mention particulière du cervelet dont l'écorce est profondément atrophiée partout; seule l'amygdale présente une préservation meilleure. Toutes les couches de l'écorce participent à l'atrophie, mais ce sont principalement les cellules de *Purkinje* et les cellules granulaires qui sont les plus raréfiées. Une spongiose assez discrète et régulière, sous la forme de petites cavités rondes, optiquement vides à toutes les colorations, témoigne de l'intensité de cette atrophie (fig. 10). Dans toutes les couches sont éparpillés de nombreux corps granulo-graisseux soudanophiles, qui n'ont aucune tendance à la confluence périvasculaire.

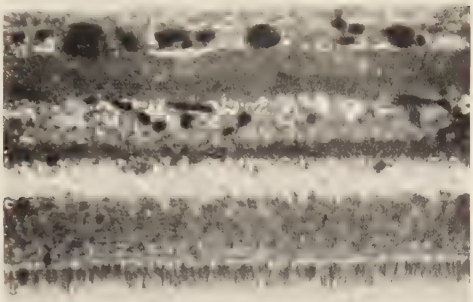

Fig. 12. Rétine. Méthode de *Smith-Dietrich*. En bas, couche des cônes et des bâtonnets intacte. En haut, couche des cellules ganglionnaires, de taille variable, bourrées de lipides.

Les cellules de *Purkinje* présentent des anomalies structurales, des tailles et des formes anormales si nombreuses qu'il y a lieu de parler de lésions dysontogénétiques (fig. 11).

En résumé, les lésions encéphaliques décrites correspondent à la forme infantile de l'idiotie amaurotique familiale. La profonde atrophie et la spongiose de l'écorce cérébelleuse, les anomalies des cellules de *Purkinje* et des cellules gliales fixent le début de l'affection très tôt dans la vie fœtale.

Examen histologique de la rétine (Dr *J. Babel*) (fig. 12).

La structure de la rétine est bien conservée presque partout. A l'extrême périphérie, les granuleuses interne et externe sont cependant confondues. Dans la région périmaculaire, la plexiforme externe est trop éosinophile et paraît épaissie (il peut s'agir là toutefois d'une légère obliquité de la coupe). Il n'y a en tout cas pas d'œdème.

Les cônes et bâtonnets, la granuleuse externe, la couche de cellules bipolaires ont une structure normale; on n'observe pas de raréfaction cellulaire.

Dans la couche des cellules ganglionnaires, on trouve, dans la région périmaculaire en particulier, des cellules spumeuses de taille variable, certaines très volumineuses. Ces cellules se retrouvent en petit nombre jusqu'à la périphérie.

Seule la couche des fibres nerveuses est atrophiée.

Diagnostic: Maladie de *Tay-Sachs*.

Commentaire

Notre cas représente une nouvelle contribution à la clinique et à l'anatomopathologie de la forme infantile de l'idiotie amaurotique. Cliniquement, l'affection s'est manifestée vers l'âge de six à sept mois par une diminution de la vivacité et une hypersensibilité au

bruit. A l'examen ophtalmologique pratiqué à neuf mois, les papilles sont pâles; la tache rouge cerise de la macula permet le diagnostic de la maladie de *Tay-Sachs*.

Au point de vue neurologique, on note une hypertonie musculaire, une hypersensibilité à la moindre excitation extérieure et des réflexes tendineux très vifs avec extension des zones réflexogènes. L'examen psycho-moteur met en évidence un gros déficit intellectuel. L'enfant reste indifférente à son entourage et se montre incapable de se tenir assise ou de soutenir sa tête.

L'*électrorétinogramme*, pratiqué à plusieurs reprises (de 9 à 28 mois), révèle aux premiers examens une *bonne réponse rétinienne*, de même importance aux deux yeux, indiquant ainsi une réceptivité normale des éléments sensoriels de la rétine et un bon fonctionnement de leurs synapses. A 23 mois, on obtient une *augmentation pathologique nette du potentiel rétinien*, en particulier de l'onde b (réponse supranormale), ce qui permet de conclure à une localisation extra-rétinienne, probablement centrale, de l'amaurose. On doit donc admettre qu'une atteinte des voies optiques ou des centres visuels corticaux est à l'origine de l'atrophie du nerf optique et de la cécité. Ceci correspond au résultat de l'électroencéphalogramme qui révèle une activité faible des régions postérieures du cerveau. Cette atrophie du nerf optique a d'ailleurs été confirmée lors de l'examen anatomo-pathologique (fig. 5), tandis que la couche des cônes et des bâtonnets s'est révélée histologiquement intacte (fig. 12).

Dans la seule observation de la littérature où une électrorétinographie a été pratiquée dans un cas de *Tay-Sachs* – celui de *Bjelkhagen* [1950] –, la fonction périphérique de la rétine ne s'est révélée que légèrement modifiée, alors que la fonction centrale apparaissait nettement altérée. Nous disposons donc dans l'électrorétinographie d'un excellent moyen de déterminer intra vitam le fonctionnement des éléments sensoriels de la rétine.

Après avoir fait un séjour de 18 mois à l'hôpital, l'enfant décédait à l'âge de 28 mois des suites de sa maladie, montrant les signes d'une «décérébration» progressive avec rigidité et cachexie.

Au point de vue *anatomo-pathologique*, l'atteinte presque totale des neurones, les modifications de volume et de forme des cellules ganglionnaires, correspondant à la dégénérescence utriculaire de *Schaffer*, et leurs réactions histochimiques font de notre cas un exemple typique d'idiotie amaurotique infantile. La névroglie se présente, en de nombreux endroits, accompagnée de curieuses

atypies de forme et de taille, résultat d'une prolifération intense et désordonnée d'astrocytes protoplasmiques munis de prolongements massifs. Le système le plus altéré est certainement le néo-pallium cérébelleux dans lequel abondent des cellules de *Purkinje* malformées et de taille exagérée. Le rapprochement entre ces caractères et les anomalies de forme de la névroglie nous amène à situer le début de l'affection dans la période fœtale, du moins en ce qui concerne le cervelet.

Les faisceaux pyramidaux sont nettement éclaircis, de même que la partie distale des axes gyraux. L'absence de corps granulo-graisseux soudanophiles de ces derniers territoires plaide en faveur d'une dysplasie des gaines de la myéline. Inversement, le grand nombre de cellules soudanophiles occupant la capsule blanche interne tendrait à prouver qu'au niveau du système pyramidal il s'agit bien d'une démyélinisation.

Le seul fait qu'il a été très rarement procédé à un examen de la *phosphatase acide* nous semble justifier la remarque que, dans notre cas, toutes les cellules ganglionnaires, astrocytaires et microgliocytaires contiennent une quantité excessive de cette substance. L'absence de ce ferment dans l'oligodendroglie confirme la non-participation de cette couche cellulaire dans le processus de thésaurismose.

Il est possible, dans notre cas, d'exclure la coexistence avec la maladie de *Niemann-Pick*, vu que le processus de surcharge épargne totalement tous les viscères examinés (foie, rate, nodules lymphatiques, ovaires, surrénales, thyroïde, hypophyse, pancréas).

Nous nous trouvons ainsi en présence d'un processus pathologique ubiquitaire et systématisé qui atteint aussi bien les cellules ganglionnaires du cerveau et du cervelet que de la rétine et qui représente le substratum anatomique de la régression psychique, motrice et sensitive observée cliniquement.

Résumé

Description anatomo-clinique d'une fillette atteinte de la forme infantile de l'idiotie amaurotique, décédée à l'âge de 28 mois. Des examens cliniques répétés ont permis de suivre la régression des facultés nerveuses à partir de 6 à 7 mois environ. L'examen ophtalmoscopique a révélé la tache rouge cerise pathognomonique de la macula entourée d'une zone grise diffuse, ainsi qu'une papille assez

pâle. L'électrorétinogramme a mis en évidence une atrophie du nerf optique secondaire à l'atteinte des voies optiques centrales ou de l'aire optique occipitale même.

Anatomiquement, les lésions ganglionnaires, névrogliques, microgliales et myéliniques sont caractéristiques de l'affection. L'existence de formes cellulaires ganglionnaires et névrogliques atypiques permet de penser que le début du processus se situe très tôt dans le développement, probablement dans la période fœtale déjà. Il est intéressant de noter la présence, en grande quantité, de phosphatase acide dans toutes les cellules nerveuses.

Summary

Anatomo-clinical description of a girl affected with infantile amaurotic idiocy and deceased at the age of 28 months. Repeated clinical investigations enabled us to observe the course of the regression of the child's psychic faculties from about the sixth to seventh month onwards. The ophthalmoscopic examination showed the pathognomonic cherry red macular spot surrounded by a diffuse grey area as well as a rather pale optic disc. The electroretinogram revealed an atrophy of the optic nerve secondary to a lesion of the central optic pathway or possibly even of the occipital visual center.

Anatomically the changes of the ganglion cells, the microglia and the myelin were characteristic of this disease. Owing to the presence of atypical ganglion and nevroglial cells, it is believed that the process has set in at a very early developmental stage, probably already during the foetal period. The presence of excessive amounts of acid phosphatase in all the nervous cells is noteworthy.

Zusammenfassung

Klinisch-anatomische Beschreibung eines mit 28 Monaten an infantiler amaurotischer Idiotie gestorbenen Mädchens. Wiederholte klinische Untersuchungen ermöglichten es, die Regression der psychischen Fähigkeiten des Kindes ungefähr vom 6. bis 7. Monat an zu verfolgen. Die ophthalmoskopische Untersuchung zeigte den pathognomonischen, von einer diffusen grauen Zone umgebenen, kirschroten Fleck in der Macula sowie eine ziemlich blasse Papille. Das Elektroretinogramm wies auf eine sekundäre Optikusatrophie hin, die infolge Befallenseins der zentralen optischen Leitungsbahnen

oder vielleicht sogar des optischen Zentrums im Hinterhauptlappen entstanden war.

In anatomischer Hinsicht erwiesen sich die Veränderungen der Ganglienzellen, Mikroglia und des Myelins als typisch für das Leiden. Das Vorhandensein von atypischen Formen innerhalb der Ganglienzellen und der Neuroglia weist auf einen sehr frühen Beginn des Prozesses hin, der vermutlich bereits auf die fötale Periode zurückgeht. Bemerkenswert ist in unserem Falle die Anwesenheit großer Mengen von saurer Phosphatase in allen nervösen Zellen.

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THOUGHTS ON THE ETIOLOGY OF CLEFTS OF THE PALATE AND LIP

By F. CLARKE FRASER

To one from whose laboratory came the definitive work on the inheritance of harelip and cleft palate, this modest contribution is respectfully dedicated.

The mammalian uterus forms a barrier to analysis of embryonic developmental errors that has, until recently, remained virtually impregnable. Several promising breaches in the barrier have been made from the rapidly growing field of experimental mammalian teratology, but so far these have not led to any clinical applications and the frequency of congenital defects in humans remains uncompromisingly high (*Fraser* and *Fainstat* [1951 a]. Little progress can be expected in the prevention of congenital defects until there is a better understanding of what causes them, and this, in turn, depends partly on a knowledge of normal developmental mechanisms.

I. Embryology of Cleft Palate

In this laboratory we have been studying palate closure in the mouse, and the ways in which it may go wrong, in the hope that analysis of this experimental model may help us to understand the results of concurrent studies in humans.

a) Normal Palate Closure

The secondary palate in the mouse normally closes in the following way (*Walker* and *Fraser* [1956]). Before closure the palatine

shelves hang down from the roof of the mouth, on either side of the tongue. In order to close they must reach the horizontal plane above the tongue, and meet in the mid-line. The process of closure involves the build-up of a force within the palatine shelves (the "shelf force") that causes them to press in toward the mid-line, against the resistance of the tongue. When the shelf force becomes strong enough to overcome the resistance of the tongue the shelves slide up over the tongue, with a wave-like movement that begins posteriorly and moves quite rapidly forward until the shelves lie in the horizontal plane above the tongue and meet in the mid-line. We can find no evidence that the jaw drops to allow the tongue to move out from between the shelves; the shelves appear rather to push the tongue down. When the shelves meet in the mid-line they fuse with each other and with the nasal septum, thus forming the secondary palate. This concept of palate closure is probably much oversimplified, and other contributory factors will no doubt be discovered, but it will serve as a working model to guide further analysis. What little evidence there is in humans (*Lazzaro* [1942]) is consistent with this concept.

b) Failure of Palate Closure

If the shelves are prevented from moving to the horizontal plane, or if they are so far apart when they do become horizontal that they cannot meet in the mid-line, a cleft palate results. *A priori*, then, one might deduce that cleft palate could occur in at least five ways.

1. An interference with the build-up of *the shelf force* may delay shelf movement sufficiently that when the shelves reach the horizontal the head is too wide to allow the shelves to meet in the mid-line, and the palate remains cleft. The cleft palates induced by maternal treatment with cortisone (*Fraser* et al. [1954]) appear to arise in this way.

2. Excessive *resistance of the tongue* may also delay shelf movement and thus cause cleft palate. We have evidence that puncturing the amniotic sac of a mouse embryo just before normal palate closure may cause cleft palate in the resulting offspring, and that this may be due to constriction of the embryo, with compression of the mandible against the anterior chest wall, thus keeping the tongue forced up between the palate shelves and so delaying shelf movement (*Walker* [1954], *Trasler*, unpublished).

3. When the shelves reach the horizontal, excessive *width of the head* will prevent their meeting. This, of course, is involved in the previous two mechanisms, where shelf movement is delayed and the head continues to grow. But even when the shelves move at the normal time it is conceivable that the head may be abnormally wide, thus leading to failure of the shelves to meet.

4. Conversely, if the *shelves are too narrow* when they reach the horizontal, a cleft palate will result.

5. Finally, it is theoretically possible that there could be a *reopening* of an already closed palate, through some degenerative process in the palatine shelves. We have attempted to confirm an earlier suggestion (*Fraser* et al. [1953, 1954]) that some cortisone-induced clefts might arise in this way, but have not been able to do so, and have therefore retracted the suggestion (*Trasler* et al. [1956]).

No doubt further analysis will reveal other factors and interrelations, but even when one considers only those discussed above it is clear that palate closure is a complicated event, involving several delicately integrated processes. Presumably each of these processes is influenced by many genetic and environmental factors. It is useless, therefore, to think of cleft palate as a single entity, or to argue about whether it is hereditary or environmental in origin.

II. Genetics of Cleft Palate in Mice

Several examples are known in mice where a change at a single genetic locus is associated with cleft palate (*Gluecksohn-Waelsch* [1954]). The incidence of "spontaneous" cleft palate in mice is low (*Trasler* et al. [1956]), and I am not aware of any marked strain differences in frequency of harelip and cleft palate. *Reed* [1936a] has shown that harelip (with or without cleft palate) is the result of multiple genetic factors interacting with multiple environmental factors. In his material most of the variation appeared to be due to intangible environmental factors, and he suggested that the situation was similar in humans (*Reed* [1936b]). Recently a number of environmental agents have been discovered which, when applied to pregnant animals, cause cleft palates in the offspring (*Fraser* et al. [1953]).

We have studied the influence of genetic factors on one such type of cleft palate—that caused by maternal treatment with cortisone (*Fraser* and *Fainstat* [1951b]). When pregnant strain A/Jax

mothers were treated with 2.5 mg. of cortisone a day for four days beginning eleven days after conception, cleft palate occured in 100% of the offspring. The same treatment in strain C57BL produced only 17% cleft palates (*Fraser* et al. [1954]), thus demonstrating the importance of the genotype in determining the organism's reaction to environmental influences.

Further analysis showed that both the maternal and foetal genotypes are important in determining the embryo's response to the teratogen. F1 hybrid embryos growing in treated A/Jax females had a 43% frequency of cleft palate, but genetically similar embryos growing in treated C57BL mothers had only a 4% frequency of cleft palate (*Kalter* [1954]). The reciprocal cross difference could have been due to a cytoplasmically inherited difference in foetal resistance to cortisone. This was ruled out by treating the two types of hybrid females backcrossed to A/Jax males, and showing that the frequency of cleft palates was the same in both groups of offspring (ibid.). It seemed that the reciprocal cross difference must therefore be due to (1) a difference in the maternal metabolism or placental transmission of cortisone, or (2) a maternally influenced difference in resistance of the foetus to cortisone.

Our present thinking favors the second possibility, since it has been shown that the palate normally closes earlier in the C57BL (resistant) embryos than in the A/Jax (susceptible) embryos (*Walker* and *Fraser* [1956]), and that in the F1 hybrids also, the palates seem to close earlier in the more resistant embryos (C57BL $\times$ A) than in the more susceptible (A $\times$ C57BL) embryos (*Trasler*, unpublished), though this is not firmly established. It may be that at least part of the strain difference in frequency of cortisone-induced cleft palate is due to a gene-determined difference in the normal pattern of palate closure.

We also know that maternal weight influences the frequency of cortisone-induced clefts, the heavier mothers having fewer offspring with cleft palates than the lighter mothers (*Kalter* [1955]). It is possible that this feature of the maternal environment might also influence the cleft palate frequency through its effect on pattern of palate closure, and we are collecting data to test this possibility.

In summary, cleft palate in the mouse can be caused by a number of different major mutant genes; it seems likely that their expression can be modified by the genetic background and environmental circumstances. In other cases cleft palate can be caused by

clear-cut environmental teratogens, such as cortisone, but again the response to the agent can be modified by the genetic background and environmental circumstances. The character "cleft palate", then, is etiologically heterogeneous and complicated.

IV. Cleft Palate and Cleft Lip in Humans

In humans there are also major mutant genes that cause cleft palates and cleft lips (*Van der Woude* [1954]) but so far no clear-cut environmental agent has been discovered that causes such defects. The excellent study of *Fogh-Andersen* [1942] has shown that, in most cases, clefts of the lip and/or palate are caused by a genetic predisposition, probably multifactorial, interacting with undefined environmental circumstances.

Several other similarities between mice and men with regard to cleft lip and cleft palate can be found.

a) Etiological non-identity of cleft palate and cleft lip (± cleft palate)

To begin with there is the non-identity of the factors for harelip (with or without cleft palate) and for cleft palate alone. In mice, the frequencies of spontaneous harelip (with or without cleft palate), cortisone-induced cleft palate and spontaneous cleft palate do not parallel each other (table 1). Similarly, in humans *Fogh-Andersen*

Table 1. Frequency of "spontaneous" harelip (with or without cleft palate), cortisone-induced cleft palate, and spontaneous cleft palate in three strains of mice.

Strain	Spontaneous harelip	Cortisone-induced cleft palate	Spontaneous cleft palate
A/Jax	high	high	low
dba	low	high	low
C57BL	low	low	low

[1942] has shown that harelip (with or without cleft palate) and cleft palate appear to be inherited separately. A similar trend was shown in our series, and the combined results are summarized in table 2.

Clearly, if the proband has a cleft palate alone, the affected relatives are much more likely to have a cleft palate alone than to have a cleft lip (with or without cleft palate). *Fogh-Andersen* also

Table 2. Type of defect in relatives of probands with cleft lip and palate (CLP), cleft lip alone (CL), and cleft palate alone (CP). Combined data of *Fogh-Andersen* and *Fraser*.

Type of defect in proband	Number of probands	Type of defect in affected relatives		
		CLP	*CL*	*CP*
CLP	464	166	107	23
CL	160	32	31	5
CP	181	16	6	51

noted that in affected relatives the proportion of cases with cleft lip alone to those with cleft lip and palate tended to be higher if the proband had a cleft lip alone (30:27 = 53%) than if the proband had a cleft lip and palate (103:138 = 43%). The combined data also demonstrate this tendency (table 2). He suggested that in most cases cleft lip and cleft lip with cleft palate are due to the same hereditary predisposition, but that in some cases cleft lip is due to a different gene that does not cause cleft lip and palate. One wonders if part of this tendency might rather be due to biased reporting, e.g. a tendency for the informant to assume the relative's defect was the same as the proband's. If one includes only affected siblings and parents in the analysis, where this bias would not be likely to occur, the numbers involved become too small to be reliable, but the same tendency appears, so there is no evidence that such a bias exists (table 3). It is also possible that the tendency is the result of a random fluctuation, having no biological significance, or that it is due to familial modifiers of the main etiological agents. (Incidentally, the independence of cleft palate alone from cleft lip [with or without cleft palate] becomes very striking when only parents and siblings are considered.)

Table 3. Type of defect in parents and siblings of probands with cleft and lip and palate (CLP), cleft lip alone (CL), and cleft palate alone (CP).

Type of defect in proband	Type of defect in affected siblings and parents		
	CLP	*CL*	*CP*
CLP	59	23	0
CL	7	5	0
CP	0	0	17

It seems clear, then, that isolated cleft palate is etiologically separate from cleft lip (with or without cleft palate), but that in our present state of knowledge cleft lip and cleft lip with cleft palate can best be considered together.

b) Maternal Age-Effects

Another way in which clefts of the lip and palate are similar in mice and men is that in both species the frequency is correlated with maternal age. In mice the frequency of cortisone-induced cleft palate decreases with increasing maternal age (*Kalter* [1955]), but this effect has been shown to depend on maternal weight, rather than maternal age *per se*. The frequency of harelip (with or without cleft palate) in mice appears to drop with increasing maternal age and then perhaps to rise again somewhat (*Reed* [1936a]).

In humans, *Fogh-Andersen* [1942] could find no association with maternal age, but *MacMahon* [1953], using a more refined statistical technique, did show such a relation. He found that (contrary to cleft palate in mice) the incidence of harelip (± cleft palate) increased slightly, but significantly, with maternal age, though there was no relation to birth order. Cleft palate alone showed no relation to maternal age or parity.

Kalter's [1955] discovery that the decrease in cortisone-induced cleft palate frequency with increasing maternal age was, in fact, a function of increasing maternal weight led us to wonder if maternal weight might be associated with frequency of cleft palate in humans (although the increasing incidence with increasing maternal age in humans would argue against this). We therefore compared maternal weight at time of conception (as stated retrospectively by the mother) in pregnancies that gave birth to a child with a harelip or cleft palate with weight at time of conception in a control series of otherwise comparable mothers giving birth to children without congenital defects. It was interesting to find (table 4) that the maternal weight at conception for all three groups of defects averaged about nine pounds lighter than that in the control group. Thus the relation of maternal weight to frequency of defect is in the same direction in humans as it is in mice. Only the difference for the cleft lip and palate group is significant at the 1% level, but if further analysis confirms that these differences are real there are several interesting implications, including a possible relation with the fact that temporary

Table 4. Weights at conception of mothers giving birth to a child with cleft lip (CL), cleft lip and palate (CLP), or cleft palate (CP), and of mothers giving birth to unaffected children

Type of defect	Numbers of mothers	Maternal weights, lbs.
CL	19	118.7
CLP	76	119.6[1]
CP	32	122.3
All clefts	127	120.1
Control	56	128.6

[1] Significantly different from the control value at the 1% level.

starvation of pregnant mice can cause cleft palates in the offspring (*Kalter* [1954]).

c) *Reciprocal Cross Differences*

The discovery of reciprocal cross differences in the frequency of cortisone-induced cleft palate in mice raised the question of whether similar maternal effects may occur in humans. If so, affected relatives would occur on the maternal more often than on the paternal side of the family. In table 5 it can be seen that in the families of

Table 5. Number of families showing a positive family history on the maternal or paternal side of the family, for cleft lip + cleft palate (CL and CLP) and cleft palate alone (CP), respectively.

Type of defect	CL and CLP		CP	
	Family History		Family History	
Source of data	maternal	paternal	maternal	paternal
Fogh-Andersen	83	63	14	13
Fraser	19	12	1	5
Combined	102	75	15	18

$p = 0.04$

probands with cleft lip (with or without cleft palate) there is a tendency for affected relatives to appear on the maternal more often than on the paternal side of the family (affected parents are excluded because the defect occurs more often in males than females). However, the difference is significant only at the 5% level, and must be regarded with caution unless confirmed by further data. One might suspect that the difference was due to the tendency of mothers to be better informed than fathers about their families, yet no such

difference occurs in the cleft palate families (table 5) or the families of epileptic probands (*Metrakos*, personal communication).

d) Frequency of Occurence in Siblings

Since our probands were obtained from the clinics and wards of The Montreal Children's Hospital and the Royal Victoria Hospital, ascertainment is neither complete nor entirely independent. We have therefore calculated the risk of recurrence of the defect in siblings in two ways: a) assuming that the *first affected child* seen in the hospital during the present study is the proband, and b) assuming that *each affected child* seen in hospital during the present study is a proband. The true frequency presumably lies somewhere between the two values so obtained. (Part of the data in this series has been published in a preliminary report—*Fraser* and *Baxter* [1954].) Table 6 presents the results on the 180 families analyzed to date.

Table 6. Risk that a sibling of a child with cleft lip $\pm$ cleft palate (CL and CLP) or cleft palate (CP) will be similarly affected.

Type of defect	Assumption[1]	Number of probands	Number of siblings	% affected siblings
CL and CLP	(a)	126	291	3.4 ± 1.1
	(b)	135	316	5.7 ± 1.4
CP	(a)	54	185	2.2 ± 1.1
	(b)	58	211	4.3 ± 1.4

[1] Assumption (a) is that the first affected child entering the series is the proband. Assumption (b) is that each affected child entering the series is a proband. Twins, and offspring of affected parents are excluded.

The results agree very well with those of *Fogh-Andersen* [1942] who found the risk for siblings of a child with cleft lip with or without cleft palate to be 4.4% (cf. our value of 3.4 to 5.7%) and the risk for siblings of a child with cleft palate alone to be 2.3% (cf. our value of 2.2 to 4.3%). We cannot agree, however, with *Reed*'s [1955] estimate of the risk of recurrence in siblings (1 in 7) which is based on the frequency of clefts in the children born after the *first affected child*, rather than those born after the proband, and is therefore, in our opinion, much too high.

e) Future Work

By analogy from the studies in experimental animals it is likely that the causes of clefts of the lip and palate in humans are not simple. Each clinical category of defect probably contains seve-

ral etiologically different types, and each type is probably determined by multiple genetic and environmental factors. We are not likely to discover any one preventive measure that will eliminate these defects.

One thing that can be done is to sort out, from the etiologically heterogeneous categories, specific types that may show different genetic patterns. For instance, a type of cleft due to an abnormally wide head (as postulated from the studies on mice) might be clinically distinguishable. (Perhaps *Fogh-Andersen*'s probands 44 and 45 would fall into this category. Both these probands, who were brothers, had very wide-set eyes, as did their mother, mother's father, and four maternal aunts.) *Van der Woude* [1954] has described a type of harelip and cleft palate associated with cysts of the lower lip, and showing a fairly simple pattern of inheritance. Identification of such entities improves the precision of the predictions we can make when counselling the families involved.

Apart from this, we can continue to search for antenatal factors that may influence whether a genetically predisposed individual does or does not get a harelip or cleft palate. Dietary and maternal reproductive factors are the ones that appear most interesting at the moment. Although no one preventive measure is likely to be found, the more of the multiple causal factors that can be identified, the better chance there is that the frequency of these defects can be reduced.

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Summary

1. Experimental studies in mice have demonstrated that congenital clefts of the palate can arise in several different ways, each influenced by multiple genetic and environmental factors.

2. The situation in humans resembles that in mice in that

a) Cleft palate alone seems to be etiologically different from cleft lip with or without cleft palate.

b) There is evidence to suggest that human mothers of children with cleft lip and/or cleft palate tend to be lighter than control

mothers. This relation is similar to that demonstrated for cortisone-induced cleft palate in mice.

c) Studies on cortisone-induced cleft palate in mice have demonstrated that the maternal genotype is important in determining the frequency of cleft palate in the offspring. A search for similar tendencies in humans has produced some evidence (at present tenuous) that such an effect may occur in the case of harelip with or without cleft palate.

3. The risk of recurrence in siblings is estimated as 3.4 to 5.7% if the proband has cleft lip with or without cleft palate, and 2.2 to 4.3% if the proband has cleft palate alone. These figures correspond closely to those found by *Fogh-Andersen* in a more extensive Danish series.

Résumé

Des expérimentations démontrent que la fissure palatine congénitale peut résulter de différentes causes, chacune étant conditionnée par de multiples facteurs héréditaires et exogènes. On peut relever de nombreux points de rapprochement entre les hommes et les souris en ce qui concerne ces difformités. Il semble par exemple prouvé que la fissure palatine isolée diffère étiologiquement du bec-de-lièvre avec ou sans fissure du palais. Certaines observations semblent suggérer que le poids des mères ayant eu un enfant avec un bec-de-lièvre et/ou une fissure palatine serait inférieur à celui d'une série de contrôle. On constate également cette particularité chez les souris où la fissure est provoquée par la cortisone. Dans ces cas-là, les examens démontrent que le génotype de la mère exerce une grande influence sur la fréquence des cas de fissure parmi la progéniture. Il est possible que cette tendance se manifeste aussi chez l'homme lorsqu'il s'agit de becs-de-lièvre avec ou sans fissure de la voûte palatine.

Le risque de bec-de-lièvre avec ou sans fissure chez les frères et sœurs puînés d'un enfant atteint de cette difformité se calcule à raison de 3,4–5,7%; s'il s'agit d'un cas de fissure isolé, le risque est de 2,2–4,3%, chiffres qui correspondent exactement aux chiffres relevés par *Fogh-Andersen* dans un rapport danois.

Zusammenfassung

1. Experimentelle Untersuchungen an Mäusen haben erwiesen, daß angeborene Gaumenspalten auf verschiedene Art und Weise ent-

stehen können, jede unter Beeinflussung mehrerer genetischer Faktoren und Faktoren der Umgebung.

b) Es sind Anzeichen vorhanden, wonach Mütter von Kindern mit Hasenscharte und/oder Gaumenspalte ein etwas geringeres Körpergewicht als die Kontrollmütter haben. Dieses Verhalten scheint das gleiche wie bei Mäusen zu sein, bei denen Gaumenspalten vermittels Cortison hervorgerufen worden sind.

c) Untersuchungen an Mäusen, bei denen Gaumenspalten mittels Cortison bewirkt wurden, haben erwiesen, daß der mütterliche Genotypus einen Einfluß auf die Häufigkeit der Entstehung von Gaumenspalten bei der Nachkommenschaft ausübt. Eine entsprechende Tendenz, wenn auch in sehr schwachem Grade, läßt sich auch beim Menschen in Fällen von Hasenscharte mit oder ohne Gaumenspalte nachweisen.

3. Die Gefahr, daß das Leiden bei Geschwistern wieder auftreten kann, wird auf 3,4 bis 5,7% geschätzt, falls der Proband Hasenscharte mit oder ohne Gaumenspalte und auf 2,2 bis 4,3%, falls er nur Gaumenspalte aufweist. Diese Zahlen entsprechen genau denjenigen, die *Fogh-Andersen* in einer größeren Versuchsreihe festgestellt hat.

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LITTLE'S SYNDROME OF FAMILIAL TYPE

(Two couples of DZ discordant twins of the same sibship)

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Today the diagnosis of "*Little*'s disease" is easily changed to that of "cerebral palsy of infancy", obviously with no great advantage, because the pathological aspects of the disease as described by *William John Little* in 1853 are well-known.

I think that the name of "*Little*'s syndrome" would be more useful because it indicates that the exogenous aetiology as proposed by *Little*, who considered the disease to be due to an abnormal delivery, is not adequate, as other factors may cause a similar syndrome.

The endogenous causes, such as the hereditary origin of *Little*'s syndrome, are among the most important factors.

This opinion is founded on many observations on families and twins. The familial observations were made by *Brower*, *Dercum*, *Vizioli*, *Clarke*, *Higier* [1911], *Tschugunoff*, *Kretschmer*, *Roger* and *Smadja*, *Wolpert*, *Lobstein*, *Higier* [1924], *Moyano*, *Araoz* and *Blanco*, *Herz*, *Litvak*, *Babonneix* and *Lange*, *Powdermaker*, *Morquio*, *D'Arrigo*, *Debler*, *Denzer*, *Pascual*, *Patzig*, *Hanhart*. The observations on twins were made by *Stiefler*, *Luxemburger*, *Laming*, *Brander*, *Curtius*, *Gebbing*, *Liebenam*, *Rosanoff*, *Smith*, *Boeters* and *Dittel*, *Nitsche* and *Armknecht*, *Nitsche*, *Thums*, *Lisch* and *Thums*, *Lamy* and others, *Guillimenet* and others, *Gedda* [1951].

In the following the author will describe a complex observation, both familial and in twins, of *Little*'s syndrome.

History of the Family

The parents, Antonio R. and Caterina R., are first cousins, being the offspring of two brothers; Antonio has been born in Sicily in 1913, and Caterina born in Piedmont in 1909. They were married in December 1939.

The first pregnancy was uneventful but the delivery occured 15 days early (January 12th, 1941), because of shock the mother suffered during the bombing of the town. The mother who, during the last month of pregnancy, suffered a slight motor deficiency of the right leg, did not know that she was carrying twins; at delivery, separated by an interval of 5 minutes a boy and a girl were born, each of whom had his own placenta. The delivery was spontaneous, but caused perineal lacerations. During the post-partum period, for three months, the mother suffered from complete functional incapacity of both legs, so that she had to stay in bed.

At birth, Francesco, the boy born first, weighed 3.800 kg.; Chiara, the girl, weighed about 1 kg. They were fed with both nurse's and cow milk.

The boy, stronger than the girl, began to walk at 13 months, while the girl only walked at 18 months, even then losing her balance easily.

Francesco started to speak normally, while Chiara talked later and from the beginning presented dysarthria. Toothing was normal in both children. At the age of three years, while the family was living in the country because of the war, Chiara suffered from an epidemic febrile disease, characterized by very high temperature and violent headaches; after one week during which these symptoms were treated with injections of quinine, the balance disturbances got worse and the feet took a club-foot position. At the Rizzoli Institute in Bologna, the diagnosis of "*Little*'s disease" was established, a tenotomy was performed and orthopedic shoes were prescribed (August 1950).

Chiara had the usual children's diseases. The first menstrual period occured at the age of 14, cycles were regular, abundant; at the same age the secondary sexual characteristics started to develop and she gained in weight.

As far as Francesco is concerned, he had a tonsillectomy at the age of 10 years and in 1954 was operated for an osseous cyst of the middle finger of the left hand; now he is in good health and passing the puberty perio d. He goes to school with good results and is very interested in the scout movement.

A second pregnancy of Caterina R. ended after a nearly normal period with a normal delivery on May 8th, 1945. The mother supposed this to be a twin pregnancy and in fact, separated by a time interval of 6 hours, two male twins were born, each with a separate placenta: first Aldo and then Oreste. These twins had mixed feedings, and Oreste, who is now nearly 11 years old has always been in good health and is going to secondary school: he has a slightly nervous temperament and suffers from nightmares.

Aldo, who at birth appeared normal though slightly smaller than his brother, during his first year suffered from an acute broncho-pulmonary process and a chronic gastro-intestinal ailment. Only at the age of 18 months he started to walk with difficulty: he has been dysarthric since he started to speak. At the age of 3 years the incoordination of movements became more and more apparent. After he was examined at the Rizzoli Institute in Bologna, the same diagnosis as for his sister was established but his condition appeared to be less severe and he was therefore not operated. For four years he went to the kindergarten which he left when he reached the age limit.

A third pregnancy of Caterina R. ended about Christmas 1948 in the 7th month, after a fall of the mother who stumbled on a stone while running in the street. After this third pregnancy two twins were born, at a time interval of a quarter of an hour, in the following order: Fabrizia, who was asphyxial and died two hours

Fig. 1. Francesco Chiara

Fig. 2. Aldo Oreste

after birth; Ferdinando, who weighed less than his sister and was 35 cm. long. The boy was able to take breast feedings but on the fourth day of life, after 24 hours of oxygen administration, he died.

Physical Examination of Chiara

15-year-old female. Her physical development is in general inferior to that of her twin (compare fig. 1). Weight and height of both children are as follows:

	Height	Weight
Chiara	1.47 m	37 kg
Francesco	1.62 m	48 kg

In the erect position, which she maintains only when leaning on something, Chiara presents herself with the thorax projected forward. Her face is rather pleasant and smiling; her eyes have an extraordinarily vivacious expression. Her speech is dysarthric and nearly unintelligible to strangers. Her relatives, however, understand her and assert that she knows a great number of words and is capable of abstractions.

The mental age is that of a child of 6 to 7 years. No sensory loss. Teeth in rather bad condition; ogival palate. The girl is very curious, would like to stay on the balcony all the time, has a sense of humor, is very affectionate, likes to contradict, is calculating and lazy. She suffers from enuresis. It is nearly impossible for her to walk without help. In the sitting position the patient appears normal. The arms present anomalies of motor incoordination and deficiency, particularly of the prehensibility of the fingers. Hyperreflexia. The legs are dragged behind. Within these limitations the patient is autonomous as far as simple actions and natural functions are concerned; she walks in the streets at the arm of adults. Nothing of interest as far as the thoracic and abdominal organs are concerned. Reaction to light of the iris slightly slow.

Orientation regarding time (yesterday, today, tomorrow) and space (different towns) is defective. Capacity for distinguishing colours is good as is also the ability to distinguish between different forms. She eats by herself and likewise takes care of her urgent necessities. At night she dreams about religious subjects.

Physical Examination of Aldo

11-year-old male. His somatic development is inferior to that of his twin (compare fig. 2). Weight and height of the twin brothers are as follows:

	Height	Weight
Aldo	1.29 m	22.500 kg
Oreste	1.40 m	34.500 kg

Aldo presents himself smiling with an open mouth from which saliva drops fairly often. The expression of his eyes is vivacious. His erect position is better than his sister's, but he, too, tries to support himself and he succeeds in walking "like a man" when, on the arm of an adult, he throws his legs forward in a gait which is similar to that of a goose. Hypotrophy of the muscles of the lower limbs. The knees have a tendency to crossing. Hyperreflexia. Slow reaction of the iris to light. Seated he appears normal as far as the posture is concerned. No sensory loss. Speech is dysarthric with a strong nasal tone; on inspection of the oral cavity an ogival palate and big adenoids are noticed; teeth in excellent condition. Nothing abnormal as far as the thoracic and abdominal organs are concerned.

Mental condition similar to that of his sister, but with a mental age of about 5 years; regarding time and space he is better oriented than his sister. Incontinence, also diurnal, of feces and urine. Nearly continuous movements without necessity and with scarce coordination of arms and legs. Athetosis. Prehensility of the hands defective but better than that of his sister Chiara.

Family History

In the family tree of the family R. (compare fig. 3) an important fact is the presence of a hereditary tendency to have twins; another twin birth occured in generation II (24, 25) with two female twin sisters, who seemed to be monozygotic (MZ) twins. The two couples which we are examining now are instead dizygotic (DZ), but the capacity of the same hereditary factor to produce MZ as well as DZ

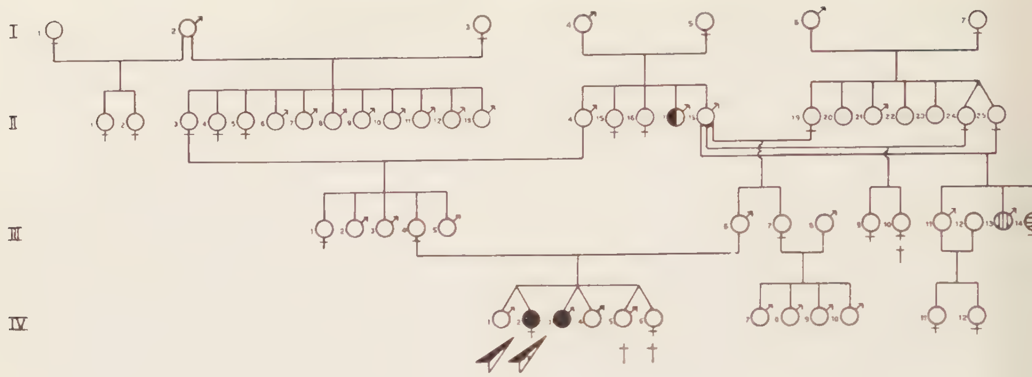

Fig. 3.

couples is well-known. Carrier of the gemellogenetic factor of this family seems to have been the paternal grandmother (II, 19).

Another important factor is the close consanguinity of the father and the mother of the patients who are first cousins. In this connection, we must also mention a male (II, 17) who died at the age of 18 years and seemed to be perfectly normal up to about the age of six years; later on he presented dyskinesia of the lower limbs, could neither stand nor walk, lost saliva, was dysarthric and seemed to be mentally defective. For this boy the probable diagnosis of *Little*'s syndrome was established.

Further we must mention a brother and sister, who are cousins of both the parents of our patients; the man is interested in astronomy and his relatives consider him slightly mentally defective (III, 13); the sister died at birth and had shown signs of facial schisis (III, 14).

Discussion

The complex case of two DZ twins not belonging to the same couple of twins but to the same sibship, suffering from *Little*'s syndrome, requires a brief comment.

First of all, it is necessary to point out the clinical symptoms of the two cases studied, which are characterized by spastic paraplegia of the lower limbs, incoordination and athetosis of the upper limbs, dysarthria and mental deficiency.

These symptoms became apparent when the children started to walk and were therefore not noticed immediately after birth.

By this we do not mean to say that clinically this is not a congenital form, because it is very probable that the malformation existed before birth and manifested itself only later after anatomical and functional development of the nerve centres. At any rate, the absence of symptoms at birth makes our cases different from those caused by an abnormal delivery which were described by *Little*.

Although the syndrome presented itself fundamentally equal in the two children, it was more severe in the female whose lower limb paralysis seemed to be more extensive than that of the boy.

The male presented greater evidence of mixed symptoms, as beside the spastic signs he had also diurnal incontinence of urine and feces, slow reaction of the iris to light, scialorrhea, restlessness and more pronounced athetosis.

Considering their age, both children were mentally retarded, but possibly less than they appeared to be, because their dysarthria made accurate evaluation difficult. From this point of view they could probably be reeducated.

We now have two problems to solve: that of the formal genesis and that of the causal genesis of *Little*'s syndrome in our two patients. As far as the causal genesis is concerned, we have the advantage of particularly favourable and significant circumstances, because our observations were made on twins of the same sibship: this fact enables us to use two methods characteristic of genetical studies, the twin method and the family method, which has not been possible in the cases described so far.

It is difficult not to think of hereditary factors as cause of the syndrome in our patients, considering 1. the fact that both patients belong to the same sibship; 2. the fact that they belong to two couples of DZ twins (i.e., twins with different heredity), and only one twin of each pair is affected; 3. the consanguinity of the parents who are first cousins: 4. the disease from which a great-uncle of the twins was suffering, who is now dead and who belongs to the cycle of consanguinity of the parents: considering the history, this illness can be interpreted as *Little*'s syndrome.

If we accept the hereditary nature of these two cases of *Little*'s syndrome, we must also admit that they support the hypothesis proposed by *Hanhart* and other authors relative to the mode of transmission, which in the family studied by us seems to be recessive.

As far as the formal genesis of *Little*'s syndrome of familial type is concerned, we think that we should not consider it an endogenous embryopathy, but rather a primary development arrest of the normal ontogenesis of the nervous system, i.e., a cerebral malformation which manifests itself clinically after birth.

This point of view coincides with the one supported by *Marie* and *von Gehuchten* in its neurological aspects, and by *Donaggio*, *Spiller*, *Fragnito*, *Finizio* in its anatomic pathological aspects.

Summary

In a sibship consisting of three pairs of dizygotic twins, two cases of *Little*'s syndrome are described. The affected persons belong to two different twin-pairs. The parents of the twins are first cousins. A great-uncle of the twins', belonging to the cycle of consanguinity of the parents, has also presented symptoms of the same kind. It is concluded that the syndrome in the family studied is a hereditary trait and that the mode of transmission is probably recessive.

Résumé

L'examen comprend un groupe de frères et sœurs comptant trois paires de jumeaux bivitellins. L'auteur décrit deux cas de maladie de *Little* – un dans chacune des deux paires. Les parents sont cousins germains. Les mêmes symptômes sont constatés chez un grand-oncle des jumeaux appartenant à la même branche de famille que les parents. On en conclut que le syndrome observé dans cette famille est héréditaire et qu'il est fort probable que la transmission en soit récessive.

Zusammenfassung

Zwei Fälle von *Little*schem Syndrom, die in zwei verschiedenen ZZ-Zwillings-Paaren in derselben Geschwisterreihe auftreten, werden beschrieben. Die Eltern sind Vetter und Cousine. Ein Großonkel sowohl väterlicher- als auch mütterlicherseits hat ähnliche Symptome aufgewiesen. Der Verfasser zieht den Schluß, daß das *Little*sche Syndrom in dieser Familie ein erbliches Leiden ist und wahrscheinlich rezessiv vererbt wird.

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AN ESTIMATE OF THE NUMBER OF Rh RECEPTORS ON A SINGLE RED CELL

By R. GRUBB

An estimate of the number of Rh receptors on a single red cell was made by *Boursnell*, *Coombs* and *Rizk* [1953], who employed sera marked with ^{131}I. In the present study an estimate was arrived at by other means, i.e., by an hemagglutination inhibition test in a system containing antihuman globulin serum and red cells coated with incomplete anti-Rh. The method has been described elsewhere (see *Grubb* [1956] for references). It was thought worth while comparing these estimates arrived at by independent methods.

Material and Methods

The properties of the incomplete *anti-Rh serum* of the *Coombs reagent* and of the *γ-globulin* preparation as well as the phosphate buffered saline used for dilutions and washings were described in detail elsewhere (*Grubb* [1956]).

The anti-Rh used contained only anti-D and had a titre of 1:1 in saline and 1:512 against trypsinized Rh-positive red cells.

The *number of red cells* was determined in a haemocytometer. It was also estimated colorimetrically after hemolysis.

The main experiments which aimed at determining the amount of γ-globulin bound by a known number of red cells from the anti-Rh were performed as follows:

Aliquots of 0.1 ml containing about 10^9 fresh red cells which had been washed 3 times were distributed among a number of tubes. 1.0 ml of dilutions of the anti-Rh was added to each tube and the

mixture incubated at 37° C for 2 hours. The red cells were then washed 7 times with about 10 ml of the phosphate buffered saline, care being taken not to remove any cells during the washing procedure. This step represented the binding of anti-Rh to the red cells. A typical experiment included 5 × 6 tubes. Anti-Rh diluted 1:4 was added to 5 tubes containing Rh-positive red cells as were also the dilutions 1:8–1:64. The sixth row contained anti-Rh diluted 1:4 and Rh-negative red cells. An additional tube contained Rh-positive cells and 1 ml buffer.

0.2 ml of dilutions of *Coombs*' reagent was then added to the red cell sediment. The dilutions of *Coombs*' reagent tested were 1:100 through 1:1600. The tubes were shaken and allowed to stand at room temperature for one hour. They were then centrifuged and the supernatant was transferred to 8 × 80 mm tubes. This step represented the absorption of antihumanglobulin antibodies. Two additional rows of tubes were added, one containing 0.5 μg γ-globulin in 0.025 ml to which 0.2 ml of the above dilutions of the *Coombs* reagent was added. The other row consisted of a twofold serial dilution series of the *Coombs* reagent and was included to check the titre of the reagent.

0.2 ml of a 0.75 per cent suspension of Rh-positive red cells coated by incubation with a 1:20 dilution of the same anti-Rh as above was then added. The tubes were then allowed to stand at room temperature for at least 2 hours and the result was read with the naked eye as described earlier (*Grubb* [1956]).

Results and Discussion

The result of an experiment carried out to estimate the amount of anti-Rh γ-globulin bound to a known number of Rh-positive cells is given in table I. In this experiment the Rh-positive cells were of type CCDe. The number of cells in each tube in the first step of the experiment had been counted to be 9.4×10^8.

As is apparent from the table the titre of the *Coombs* reagent that had not been in contact with coated red cells was 1:25,600. 0.5 μg γ-globulin inhibited the anti-human γ-globulin antibodies contained in 0.2 ml of the 1:800 and higher dilutions of the reagent. The same effect was obtained by about 10^9 red cells that had absorbed anti-Rh from the 1:4 and 1:8 dilutions. Cells that had absorbed anti-Rh from the higher dilutions were less active as

Table I. Absorption of Dilutions of Anti-Human-Globulin Serum by Red Cells Coated with Incomplete Anti-D and by Human γ-Globulin. The results of the subsequent agglutination tests are recorded.

The dilutions of anti-human globulin serum were absorbed with	Dilutions of anti-human globulin serum 1:100	200	400	800	1,600	3,200	6,400	12,800	25,600	51,200
Rh+ cells incub. with anti-D 1:4	+	+	(+)	—	—					
Rh+ cells incub. with anti-D 1:8	+	+	.+.	—	—					
Rh+ cells incub. with anti-D 1:16	+	+	+	.—.	—					
Rh+ cells incub. with anti-D 1:32	+	+	+	+	—					
Rh+ cells incub. with anti-D 1:64	+	+	+	+	(+)					
0,5 μg γ-globulin	+	+	.+.	—	—					
Rh— cells incub. with anti-D 1:4				+	+	+	+	+		
Rh+ cells incub. with buffer								+		
Not absorbed (control titration)	+	+	+	+	+	+	+	+	(+)	—

inhibitors. No inhibition was observed in the series in which the *Coombs* reagent had been in contact with Rh-negative cells that had been incubated with the anti-Rh.

This experiment was repeated several times also with cells presumably heterozygous with regard to D, and the results obtained resembled those recorded in the table. Owing to the considerable error inherent in the method (agglutination in a twofold serial dilution) this similarity is hardly evidence that the amount of antibody absorbed by red cells from homozygous and heterozygous persons is the same.

The quantitative relationships in this inhibition system was studied earlier and it was found that the amount of γ-globulin (or serum protein) causing inhibition is almost exactly inversely proportional to the amount of *Coombs* reagent used (*Allison* and *Morton* [1953], *Grubb* [1956]).

The result of the experiment tabulated above is taken to indicate that the stated number of red cells can bind about 0.5 μg of anti-Rh demonstrable by the method employed.

The data obtained permit estimation of the number of Rh-receptors on a single red cell. This estimate is, however, based on certain assumptions. *Boursnell*, *Coombs* and *Rizk* commented on the assumptions a) that a single antigen site combines with a single antibody molecule, b) that all available sites are satured when no further antibody is absorbed, c) that there is no loss of antibody

in the washings, d) that the molecular weight of anti-Rh as of most other γ-globulins is about 165,000. These assumptions apply not only to the present method of study but also to the use of isotope labelled sera. An assumption of the degree of iodination of the antibody molecules is circumvented by the present method but another assumption is introduced: that all the anti-Rh antibody molecules that are bound to the red cells from the serum used are active as inhibitors of the anti-humanglobulin antibodies. This assumption may or may not be true. For this reason this estimate of the number of Rh-receptors should preferably be regarded as a minimum value. If these assumptions are accepted the number of Rh-receptors on a single red cell can be computed from the expression $\frac{W \cdot N}{M \cdot R}$ where W = weight in gram of antibody absorbed (in the present case $0.5 \cdot 10^{-6}$); N = Avogadros number ($6.02 \cdot 10^{23}$); M = molecular weight of antibody (165,000) and R = number of red cells. The value obtained by the present method amounts to about 2000. This number, which is regarded as a minimum value is of the same order as that (5500) arrived at by *Boursnell*, *Coombs* and *Rizk*.

Summary

The number of Rh-receptors on a single red cell was estimated by means of a hemagglutination inhibition test. The estimate, which is regarded as a minimum number, amounts to a few thousand.

Résumé

Le nombre de récepteurs Rh d'un seul globule rouge, estimé par une réaction inhibitive d'hémagglutination, s'élève à quelques milliers.

Zusammenfassung

Die Anzahl der Rh-Rezeptoren eines einzigen roten Blutkörperchens wurde mittels eines Hämagglutinationsinhibitionstestes auf einige Tausend geschätzt.

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VARIATION IN HOMOZYGOUS CYSTINURIA

By H. HARRIS and ELIZABETH B. ROBSON

It has become possible to differentiate on genetical grounds between two main forms of classical cystinuria. One of these appears to be recessive and the other incompletely recessive (*Harris, Mittwoch, Robson* and *Warren* [1955 b]). In both cases the affected homozygotes are characterized by the excretion in their urine of large amounts of the four aminoacids; cystine, lysine, arginine and ornithine. This is probably due to a specific disturbance in the renal tubular reabsorption of these substances from the glomerular filtrate.

The homozygotes of the two types do not on the average differ very greatly from one another in either the quantity or relative proportions of the four aminoacids excreted. In consequence no satisfactory basis for the differentiation of the two types of homozygote by purely biochemical studies on individual cases has yet been found. In both forms of the condition, however, considerable variation in the relative proportions of the different aminoacids excreted may be observed from case to case, and it is the purpose of this paper to examine, in a preliminary manner, how far such variation is genetically determinated and what its significance may be.

A convenient index of this variation in pattern of excretion is the ratio of the quantity of lysine to the quantity of arginine found in individual urine samples. Among homozygotes of the recessive type, values for this ratio as high as 4.2 and as low as 0.8 have been observed in different individuals. Such large differences are greater than can be reasonably attributed to experimental error in the aminoacid estimations. Furthermore, repeated determinations on different samples from the same individual over a period of some

months suggest that a relatively high or a relatively low ratio is likely to be an individual characteristic.

When we began to examine our existing data from this point of view a rather unexpected phenomenon was observed. The variation in the lysine/arginine excretion ratios was very much greater among the homozygotes of the recessive type than among those of the incompletely recessive type. The distribution of this ratio among 48 different individuals, all believed to be homozygous for one or other of the genes involved, is shown in Table I. They have

Table I. Distributions of Lysine/Arginine Excretion Ratios in 48 Presumed Homozygotes, Classified into the Recessive and Incompletely Recessive Types.

Value of lysine/arginine ratio	Recessive Homozygotes	Incompletely recessive Homozygotes	Total
4.5–	1	0	1
4.0–	2	0	2
3.5–	0	0	0
3.0–	5	1	6
2.5–	2	0	2
2.0–	6	2	8
1.5–	1	9	10
1.0–	6	5	11
0.5–	7	1	8
0.–	0	0	0
Total	30	18	48
Mean	2.1	1.7	2.0
Variance	1.3	0.3	1.1

been classified into the recessive and incompletely recessive types on the basis of the family investigations in each case (*Harris* et al. [1955b]). The variance in the recessive group is more than four times that in the incompletely recessive group and the effect is almost certainly a significant one (Variance Ratio = 4.3, df = 29, 17, P < 0.01). The means for the two groups are, however, not significantly different (d = 0.4, P > 0.1 using *Welch*'s test (*Pearson* and *Hartley* [1954]), though that for the recessives is somewhat greater than that for the incompletely recessives.

Two questions therefore present themselves. Why do we observe such large variations in excretion pattern among individuals thought

to be of the same genotype? Why is the variation so much greater among the recessive homozygotes than among the incompletely recessive ones?

One approach to these problems is to examine the degree of likeness between affected sibs with respect to the particular variable under consideration. The absence of any appreciable correlation between sibs in any one group of cases would suggest that the variation in the lysine arginine excretion ratio was largely due to environmental factors, or to experimental error in the assay of the individual aminoacids. A significant positive correlation, on the other hand, would suggest that genetical factors were probably involved, although it is true that, in rather special circumstances, environmental differences between families might lead to some degree of sib-sib correlation. Where a positive correlation can be reasonably attributed to genetical causes, then the value of the correlation coefficient may give some indication of the nature of the factors involved. This kind of situation was discussed by *Haldane* [1941] with respect to the analysis of the genetical factors responsible for the variation in age of onset a number of different hereditary diseases. The same line of argument may be applied here. If the variation were due to a number of common modifying genes which affected the mode of manifestation of the main gene causing the disorder, then the correlation between affected sibs should approach 0.5. On the other hand, the variation may be due to the existence of a number of different rare genes which would give a series of distinct conditions sufficiently similar to one another to be classified together, but differing slightly in one or more of their detailed characteristics. With respect to any one of these variable characters the expected sib-sib correlation would approach 1.0. It may in practice be difficult to distinguish between these situations using such a model (*Harris* and *Smith* [1949]). Nevertheless the method of approach is sufficiently interesting to be worthy of trial where the appropriate data can be collected.

Material and Methods

In a review of our series of families in which cystinuria is known to be segregating, we were able to select thirteen different sibships relevant to this investigation and still available for study. In each of these sibships there occured at least two individuals who excrete

Table II. Data on Sib Pairs.

Family No.*	Sex	Age	mg. lysine / g. creatinine	mg. arginine / g. creatinine	mg. lysine / mg. arginine
Recessive Homozygotes					
Cy 7 II. 5	F	34	715	287	2.49
II. 7	M	27	938	362	2.60
Cy 17 II. 1	M	29	1583	720	2.20
II. 4	M	19	874	402	2.18
Cy 22 II. 1	F	24	876	273	3.21
II. 3	M	19	956	283	3.38
Cy 23 III. 7	M	42	496	358	1.39
III. 5	M	47	1168	1146	1.02
Cy 34	M	22	839	260	3.22
	F	30	1153	247	4.66
Cy 40	M	8	1070	314	3.41
	M	6	2413	703	3.43
Cy 42	F	19	801	425	1.89
	F	40	441	462	0.95
Incompletely Recessive Homozygotes					
Cy 1 III. 2	F	27	465	288	1.62
III. 4	F	21	1057	455	2.32
Cy 29 II. 6	M	27	1659	1215	1.36
II. 2	M	34	1504	832	1.81
II. 4	M	32	1040	612	1.70
Cy 36	M	9	1561	807	1.93
	M	14	1231	821	1.50
Cy 37	M	25	1341	726	1.84
	F	15	2271	1724	1.32
Cy 38	M	46	539	581	0.93
	F	36	727	427	1.70
Cy 43	M	16	1796	1249	1.44
	F	9	800	736	1.09

* Numbers up to Cy 29 refer to the pedigrees published in *Harris* et al. [1955 b]. Families Cy 30 to Cy 43 are unpublished.

large amounts of cystine, lysine, arginine and ornithine. The reasons for believing these individuals to be homozygotes and the grounds by which they may be classified into the recessive and incompletely recessive types of condition have been given in detail elsewhere (*Harris* et al. [1955b]).

In each case the lysine and arginine excretion was reinvestigated, using the same methods of microbiological assay as those described previously (*Harris*, *Mittwoch*, *Robson* and *Warren* [1955a]). The only difference from our previous procedure was to carry out twice as many replications for each assay in order to cut down the variance due to experimental error as far as was conveniently possible. Creatinine determinations were also carried out in accordance with our usual procedure.

The relevant data on the sets of affected sibs are given in Table II. Fig. 1 shows the sib-sib correlation diagram with respect to the lysine/arginine excretion ratio. It is apparent that there exists a relatively high sib-sib correlation in the data taken as a whole, but that this is largely accounted for by the sib pairs from the recessive group of cases.

Haldane [1941] and *Fieller* and *Smith* [1951] have pointed out that the correlation between sibs is probably best treated as an

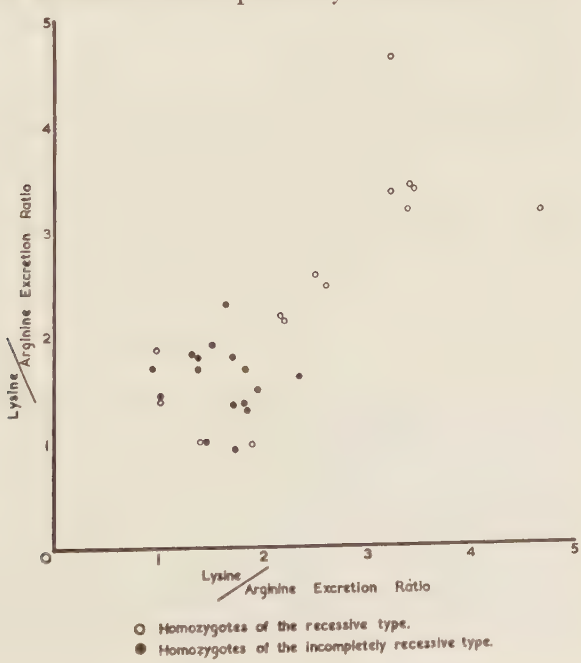

Fig. 1. Correlation diagram of the lysine/arginine excretion ratio in pairs of sibs homozygous for cystinuria.

Table III. Analysis of Variance in Lysine/Arginine Excretion Ratios in Affected Sibs of the Recessive Type.

Source of variation	D. F.	Sum of squares	Mean square
Between classes	6	12.942	2.157
Within classes	7	1.562	0.223

Variance ratio = 9.67 $P < 0.01$

analysis of variance, the variance within sibships being small compared with that between sibships when r is high. The significance of the effect may be examined by the variance ratio test. The analysis of variance for the sibships of the recessive group is given in Table III and that for the incompletely recessive in Table IV. In the recessive

Table IV. Analysis of Variance in Lysine/Arginine Excretion Ratios in Affected Sibs of the Incompletely Recessive Type.

Source of variation	D. F.	Sum of squares	Mean square
Between classes	5	0.691	0.138
Within classes	7	0.951	0.136

Variance ratio = 1.01 $P > 0.2$

group there is a highly significant variance ratio. This corresponds to an ordinary intraclass correlation coefficient of 0.90, (*Fisher*'s $z = 1.47 \pm 0.43$), or to one of 0.81 according to the modified version of *Fieller* and *Smith* [1951]. In the incompletely recessive group, on the other hand, there is no indication of any appreciable sib-sib correlation at all ($r = 0.01$ by both methods, $z = 0.01 \pm 0.49$).

Discussion

In view of the rather small number of suitable sibships available for study, any conclusions drawn can at best be only tentative. Nevertheless the difference observed between the group of recessive sibships and the incompletely recessive ones is very striking, and is likely to be of some biological significance.

The absence of any appreciable sib-sib correlation in the incompletely recessive group presumably means that most of the variation in the lysine/arginine excretion pattern encountered

there is non-genetical in character. On the other hand, the highly significant sib-sib correlation in the recessive group suggests very strongly that the variation in excretion pattern found there is largely due to genetical causes. The possibility that there may exist environmental circumstances, peculiar to some sibships and not to others, which are capable of producing an effect of this size seems unlikely.

If one accepts the view that the variation in the recessive group is indeed largely genetical, then one may attempt to distinguish between the possible mechanisms which might give rise to it. Common modifying genes affecting the manifestation of the main gene in homozygotes would be expected to lead to a sib-sib correlation approaching 0.5. A series of different rare genes (possibly alleles) each capable in homozygous form of giving rise to the syndrome which we have called recessive cystinuria, but each with a slightly different lysine arginine excretion pattern, would be expected to give rise to a sib-sib correlation approaching 1.0. In both cases one would expect that the observed correlation would fall short of that theoretically expected because of other sources of variance such as experimental error in the assays. Consequently the value for the sib-sib correlation in the recessives of 0.90 is rather in favour of the idea that more than one rare main gene can give rise to this condition. The data, however, are too small for us to distinguish critically between a correlation coefficient of 0.90 and, say, one of 0.4, and so the possibility of multiple common modifiers cannot be excluded. It is perhaps worth noting that such modifiers, if they were the main cause of the variation in the recessive homozygotes, could presumably have very little effect in influencing the manifestation of the gene in the incompletely recessive homozygotes.

These results also pose new problems in terms of the underlying physiology of the condition. The excretion of cystine, lysine, arginine and ornithine in large amounts is believed to be due to a specific failure in their renal tubular reabsorption from the glomerular filtrate (*Dent* and *Rose* [1951], *Fowler*, *Harris* and *Warren* [1952], *Dent*, *Heathcote* and *Joron* [1954], *Dent*, *Senior* and *Walshe* [1954]). If such a failure in tubular reabsorption were complete and the renal clearances for each of the aminoacids involved were the same as the rate of glomerular filtration, then presumably significant differences in the proportions of the aminoacids excreted would reflect differences in their plasma levels. However, recent studies (*Arrow* [1955], *Rose*

[1955]) suggest that the clearances of some of these aminoacids in homozygotes are often significantly less than the glomerular filtration rate. Apparently some tubular reabsorption of these aminoacids still occurs, and so it is quite possible that the variation in the detailed pattern of aminoacid excretion reflects variations in the character of residual tubular activity, rather than differences in plasma levels. The matter can only be resolved by clearance studies in individuals with markedly different excretion patterns.

Thus, although a number of different interpretations are possible, the data taken as a whole are consistent with the idea that what we have called homozygous recessive cystinuria may be due to a number of separate rare genes which may or may not be allelic. The affected individuals would be either homozygous for one of these genes, or heterozygous for two of them. In each case there is a gross failure in the renal tubular reabsorption of cystine, lysine, arginine and ornithine, but the detailed character of the excretion pattern varies from one to the other, possibly because each gene influences tubular activity in a slightly different way. There is no indication of any similar heterogeneity in the incompletely recessive form of the condition.

One can perhaps think of the situation in terms of the following model. If the basis of the process of reabsorption of the four aminoacids in the normal subject were their common transport across the tubule cells by a specific substance whose character was determined by the normal allele, then the mutant genes might each lead to the synthesis of an abnormal variant of this carrier substance. Such variants might not only be far less efficient than their normal counterpart in their capacity to transport the aminoacids, but could also conceivably have somewhat different relative affinities for the four aminocids with which they were concerned. This could lead to the detailed differences in pattern of excretion observed. Such ideas are of course highly speculative but are of interest because of their analogy with the well known effect of a series of different genes on the structure and properties of a single substance of physiological importance—haemoglobin.

Summary

The lysine/arginine excretion ratio has been studied in 48 individuals thought to be homozygous for classical cystinuria. The

variance in this ratio was found to be much greater in the recessive type than in the incompletely recessive type, but the means did not differ significantly. A correlation coefficient of the value 0.90 was observed in sib pairs of the recessive type, but no correlation could be demonstrated between sibs of the incompletely recessive type. These results were interpreted as meaning that the variance in the first type is largely genetical in origin, whilst that in the second type is almost entirely environmental. The high value of 0.90 is taken to indicate that the condition which we have called recessive cystinuria probably consists of a number of different conditions caused by separate rare recessive genes. No such heterogeneity is indicated in the incompletely recessive type. These results are discussed in terms of the underlying physiology of the condition.

Résumé

La relation excrétion lysine/arginine a été étudiée chez 48 individus considérés comme homozygotes pour la cystinurie classique. La variation dans cette relation est beaucoup plus marquée dans le type récessif que dans le type incomplètement récessif, mais il n'existe pas de différence significative dans les valeurs moyennes.

Un coefficient de corrélation de 0,90 a été observé chez des paires de sœurs et de frères du caractère récessif, mais il n'a pas été possible d'établir une corrélation dans les fratries du caractère incomplètement récessif.

De ces résultats on a conclu que la variation dans le premier type est d'origine principalement génétique, tandis que celle du second type est presque entièrement due aux facteurs extérieurs.

La valeur élevée de 0,90 semble indiquer que, dans l'affection appelée par nous cystinurie récessive, plusieurs facteurs entrent en jeu, qui sont dus à des gènes séparés et rares du type récessif. Dans le type incomplètement récessif, il n'existe pas de telle hétérogénéité.

Ces résultats sont discutés par rapport aux manifestations physiologiques de l'affection en cause.

Zusammenfassung

Das Verhältnis der Lysin/Arginin-Ausscheidung wurde an 48 Personen, die als homozygot für die klassische Cystinurie betrachtet werden, studiert. Die Schwankungen dieses Verhältnisses waren in

den rezessiven Typen viel größer als in den unvollständig rezessiven; die Mittelwerte waren jedoch nicht wesentlich verschieden. Ein Korrelations-Koeffizient von 0,90 wurde in Geschwisterpaaren von rezessivem Typus beobachtet, doch konnte keine Korrelation bei Geschwistern von unvollständig rezessivem Typus festgestellt werden.

Diese Resultate werden dahingehend interpretiert, daß die Veränderung im ersten Typus hauptsächlich genetisch bedingt ist, die im zweiten Typus dagegen fast ausschließlich durch die Umgebung bewirkt wird.

Der hohe Wert von 0,90 weist darauf hin, daß in der von uns als rezessiv bezeichneten Cystinurie wahrscheinlich eine Anzahl verschiedener Faktoren zusammenwirkt, die durch separate, seltene und rezessive Gene bedingt sind. Eine derartige Heterogenität tritt in dem unvollständig rezessiven Typus nicht auf.

Die Resultate werden unter Bezugnahme auf die der Störung zugrunde liegenden physiologischen Erscheinungen diskutiert.

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A STUDY OF PSYCHOTIC PATIENTS OF CONSANGUINEOUS PARENTAGE

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We are indebted to the medical superintendents of the Blakstad, Nevengaarden, Presteseter and Sanderud Mental Hospitals (Dr. *J. W. N. Horneman*, Professor *F. Rud*, Dr. *L. Madsen* and Dr. *A. Haugen*) for giving us access to the medical records of their hospitals, and for the kind hospitality extended to us and our assistants.

According to traditional, now almost classical, teachings, the inheritance of functional psychoses is comparatively simple: *Kraepelin*'s two major *clinical* entities of dementia praecox and manic-depressive insanity are assumed to correspond to *genetic* entities, determined by major genes according to a relatively simple *Mendelian* formula. The considerable number of individual cases which do not conform to this system, is dealt with either as mixed psychoses, caused by heterogeneous inheritance (*J. Chr. Smith* et al.), or as intermediate forms (Rand-Psychosen, *Kleist*) which will by and by be singled out as smaller but still specific genetical-clinical entities. For the typical (nuclear, central) cases, the "Kerngruppen", the hypothesis is that in schizophrenia the inheritance is mainly (or even simply) recessive, while in manic depression it is dominant.

In clinical psychiatry it has become increasingly clear that this useful system represents an over-simplification, and the nosological hypothesis has had to be modified along dynamic or multi-dimen-

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sional lines (*E. Bleuler*, *Adolf Meyer*, *E. Kretschmer* etc.) Even from the point of view of genetics a more complex solution has become likely. With particular reference to the hypothesis of simple dominance it has been pointed out that in the interpretation of data from proband investigations the influence of statistical errors has probably been underestimated. It has been shown that the incidence of schizophrenia is about four times as high in the single as in the married, while no similar difference exists for manic-depressive psychosis. This will naturally influence the findings in parents and siblings of probands so as to suggest recessive inheritance in schizophrenia and dominant in manic depression.

Consanguinity offers a possible approach towards the solution of this problem: In what way, if any, do psychotic patients whose parents are first cousins differ from the average? In Norway admission to mental hospitals depends upon a medical certificate. One of the questions on the admission form is: Are the parents of the patient related to each other? Generally the form is carefully filled, in most cases by a public health officer or a specialist in psychiatry—although it is often evident that historia morbi and status praesens have interested the doctor more than has the family history. In the overwhelming majority of cases this particular question is answered, however, and theoretically the doctor should be in a position to answer it correctly. He is supposed to contact the patient's next of kin whenever possible, so as to obtain a complete case history in confirmation of what the patient himself is able to tell, and in Norway most people have a fairly complete knowledge of their grandparents. It was, therefore, considered possible to collect from the admission forms and the case histories in our mental hospitals a material of the type indicated above. Four hospitals in Eastern Norway and one in Bergen were chosen, and the admission forms and case histories of 11145 first admissions from the period of 1926–1955 were examined. The result was 126 cases in which the parents of the patient were first cousins, 63 men and 63 women.

The rate of consanguinity in different parts of Norway is not known, but Swedish data suggest around two per cent in typically rural districts and one per cent or less in cities. In our material the consanguinity rate among the first admissions is very nearly the same in the four eastern hospitals, and it is also the same for cities as for urban districts (0.89 per cent as against 0.90). The western hospital receives patients from the city of Bergen (with 100 000 in-

habitants, the second largest city in Norway) as well as from the entirely rural county of Sogn and Fjordane. Here we find a consanguinity rate of 0.90 per cent for Bergen and 3.4 per cent for the county. The striking difference between this western county and the eastern rural districts most likely reflects a corresponding difference in the consanguinity rate of the general population, as small isolates are much more common in the western fjord districts than in the agricultural east.

It is generally assumed that the consanguinity rate is decreasing rapidly because of the breaking up of isolates. In our material the admissions from the first half of the period of investigation (1926–40) show a consanguinity rate of 1.42, as against only 0.89 for the last fifteen years. It is our impression, however, that this decrease is in part due to the increasing number of admissions by psychiatric specialists, who tend to take the admission forms less seriously.

On the whole, the consanguinity rate we have found among the first admissions cannot be regarded as suspiciously low. Most likely it corresponds fairly well to the rate in the general population. Now it might be argued that among the insane an abnormally high incidence of consanguinity would be expected, but as to this very little actual information is available. *Malzberg* states that in two samples of schizophrenics 5 per cent were found to come from consanguineous matings, but the degree of consanguinity is not given. In our material the schizophrenics alone give a percentage of 1.2, as against 2.4 for the manic-depressives.

As an attempt at control, personal letters were written to the relatives of 331 patients admitted in recent years to one of the four eastern hospitals. An answer was received from 81.9 per cent, but no information of consanguinity not already known from the admission forms or the case histories was obtained. Our sample may therefore be regarded as being not far from complete. The danger that it should not be representative is, under such circumstances, very small, and besides it is hardly conceivable that the clinical picture of a functional psychosis should have any bearing upon the tendency to answer this particular question. Possibly our information is more complete in cases where the disorder is supposed to be, or known to be, of a hereditary nature, while for instance in general paresis and in many organic psychoses this question on the admission form is more likely to have been neglected. Also in very old patients the information one can get about their parents is likely to

be less complete. These possible errors are irrelevant, however, as organic and senile cases are for other reasons excluded from our analysis (see below).

The "consanguineous group" of 126 patients is now compared with a control material consisting of 202 patients which have (in connection with another proband investigation) been selected at random among the first admissions to two of the four eastern hospitals in question. In this control material all organic psychoses, idiots and imbeciles and finally cases with age at onset above 65 years were excluded—otherwise the two groups should be comparable. In particular they date from approximately the same period.

Both groups have been treated exactly alike: Complete abstracts from the case histories were prepared by trained medical assistants or by us. In some instances the information obtained from the hospital records could be supplemented by a follow-up

Table I. Revised Diagnosis in Consanguineous and Control Groups

	Consang.	Contr.	$\frac{d^2}{m}$
1. Schizophrenia	42	62.0	3.82
2. Schizophrenia, doubtful and borderline	7	2.7	
3. Manic-depressive psychosis	26	10.6	22.38
4. Reactive (psychogenic, with constitutional psychopathic inferiority).			
a) Depressive forms (reactive depr.)	21	11.1	8.83
b) Paranoia and paranoid forms	5	9.5	2.13
c) Hysterical and confusional forms	5	11.1	2.34
d) Other and indefinite forms	1		
Comparable diagnostic groups	107	107.0	39.50
χ^2 for heterogeneity	25.15	:	$p < 0.001$
5. Psychosis with mental deficiency	8		
6. Organic psychoses	11		
	126		

As the expected values are calculated from a control material of only 202 cases, $S\left(\frac{d^2}{m}\right)$ represents an overestimation of χ^2, which therefore is given for heterogeneity. The latter values for χ^2, however, may possibly be spuriously low as our two groups cannot really be regarded as *equivalent* samples, but are drawn from the hospital population according to different principles: The control group represents the total hospital population, while the consanguineous group represents a rather special one-per cent fraction of this total population.

examination. Now all cases were classified and coded by one of us personally (*Ødegård*), and every attempt was made to keep the evaluation uniform. Most patients could not be personally examined, and in many cases the information was rather incomplete. The clinical analysis has, therefore, been restricted to comparatively simple and superficial data, and too subtle classifications have been avoided.

A comparison between the consanguineous group and the control material (see tables) reveals a series of significant differences, which add up to a fairly definite pattern. In the consanguineous group there is more manic-depressive insanity and less schizophrenia, and within the heterogeneous group of "reactive" psychoses (psychogenic, with constitutional psychopathic inferiority), the depressive forms predominate over the paranoid. Psychiatric diagnosis being what it is, it seemed useful to check up on this finding by the use of criteria which may be somewhat more objective, or at least more purely descriptive.

Table II. Predominant Syndrome in Consanguineous and Control Groups

	Consang.	Contr.	$\frac{d^2}{m}$
Depression	39	19	21.01
Excitement	14	5.8	
Confusion	2	4.3	0.90
Hysterical, compulsive, neurasthenic	2	4.3	
Paranoid	14	28.6	6.76
Paranoic	6	6.9	
Hebephrenic	14	24.3	4.37
Catatonic	16	13.8	0.35
Total	107	107	33.39
χ^2 for heterogeneity	20.02	:	$0.01 > p > 0.001$

Using at first the predominant *syndrome* as a basis for our classification, we find in the consanguineous group an excess of depressions and excitations, while paranoid and hebephrenic pictures are relatively more rare, and catatonic conditions are about equally common in both groups.

An analysis according to the predominant *symptoms* shows that in the consanguineous group the disturbance of mood and affectivity tends to take the form of depression or elation, while irri-

Table III. Predominant Affective Symptoms in Consanguineous and Control Groups

	Consang.	Contr.	$\frac{d^2}{m}$
Depression	45	30.1	7.38
Elation, euphoria	19	10.6	6.66
Anxiety	6	6.9	0.12
Temper tantrums	8	15.4	3.56
Instability	6	10.6	2.00
Apathy	16	17.0	0.06
Perplexity	–	6.4	
Irritability	3	7.4	5.38
No marked affective disturbance	4	2.6	
Total	107	107	25.16
χ^2 for heterogeneity	16.38	:	$0.01 < p < 0.02$

tability, temper tantrums and perplexity are relatively less common. Anxiety and apathy do not present any differences. Hallucinations (particularly auditory) are less common in the consanguineous group, while psycho-motor symptoms appear to be equally common in both. In the consanguineous group the delusions tend to be self-deprecatory or grandiose, while ideas of reference and persecution are relatively more rare.

As to the *course of the illness* we find that in the consanguineous group the initial stage is more frequently coloured by transitory episodes or by a change of personality and character, while ideas of

Table IV. Predominant Psychomotor Symptoms in Consanguineous and Control Groups

	Consang.	Contr.	$\frac{d^2}{m}$
Inhibition	15	12.2	0.64
Blocking, stupor	16	13.3	0.55
Mannerisms	8	12.2	1.45
Excitement	32	30.7	0.06
Agitation	15	14.3	0.03
Varying symptoms	–	5.8	
No predominant psychomotor symptoms	21	18.5	0.45
Total	107	107	3.18
χ^2 for heterogeneity	2.51	:	$0.8 > p > 0.7$

Table V. Predominant Content (Delusions) in Consanguineous and Control Groups

	Consang.	Contr.	$\frac{d^2}{m}$
Self-accusatory	27	18.1	4.38
Hypochondriasis, financial worries	13	11.–	0.36
Ideas of reference	4	9.–	2.78
Persecutory	24	35.–	3.45
Grandiose	18	10.6	5.16
Revendication, jealousy	6	4.8	0.30
No predominant content described	15	18.5	0.66
Total	107	107	17.09
χ^2 for heterogeneity	10.95	:	$0.10 > p > 0.05$

reference or religious and philosophical preoccupations are less common. Depressive and neurasthenic pictures are (in the initial stages) equally common in both groups. In the consanguineous group acute onset and a periodic course with good or fair remissions predominate, while in the control material the tendency is towards subacute or insidious onset and a development towards moderate deterioration.

Cases with an intermittent course naturally tend to have more than one admission during the period of investigation. This may represent a source of error if additional and more complete information on consanguinity becomes available *because of the re-admissions*. In one of our 126 cases the information that the parents were first cousins was found on the second admission form, while on the first form this particular question was not answered. This must be regarded as exceptional, however, and in most cases the family history is not even mentioned when a patient is re-admitted.

Table VI. Hallucinations in Consanguineous and Control Groups

	Consang.	Contr.	$\frac{d^2}{m}$
Auditory	29	40.2	3.12
Other forms (visual, somatic etc.)	2	15.4	11.65
Multiple	24	26.4	0.22
No predominant hallucinations	52	25.0	29.19
Total	107	107	44.18
χ^2 for heterogeneity	20.83	:	$p < 0.001$

Table VII. Predominant Initial (Prodromal) Symptoms in Consanguineous and Control Groups

	Consang.	Contr.	$\frac{d^2}{m}$
Transitory episodes	27	6.9	58.60
Change of character and personality	21	13.3	4.46
Depression	22	21.1	0.04
Neurasthenic, psychosomatic	17	16.–	0.06
Ideas of reference	2	20.7	16.89
Emotional outbursts, tantrums	1	9.5	7.60
Religious and philosophical preoccupations	4	9.5	3.18
Nothing special registered	13	10.–	0.90
Total	107	107	91.73
χ^2 for heterogeneity	48.01	:	$p < 0.001$

Etiological factors were not very completely dealt with in the hospital records and therefore the data are omitted. What information there is, seems to indicate that in the consanguineous group personality deviations as well as mental conflicts or maladjustment play a relatively less important role than in the control material. The general level of intelligence seems to be about the same, and there is no difference with regard to abuse of alcohol.

These findings are hardly consistent with the current hypothesis of recessive inheritance in schizophrenia and dominant in manic depression. They suggest, in fact, that recessive inheritance may be *relatively* more important for the affective psychoses than for the paranoid and deteriorating types. The term relative is

Table VIII. Onset and Course of Illness in Consanguineous and Control Groups

	Consang.	Contr.	$\frac{d^2}{m}$
Acute, without prodromes	14	13.3	0.04
Acute, after prodromes	16	10.–	3.60
Sub-acute	18	26.–	2.46
Insidious, with exacerbations	16	17.4	0.11
Insidious	13	20.1	2.51
Episodic	5	4.3	4.75
Periodic (intermittent)	25	15.9	
Total	107	107	13.47
χ^2 for heterogeneity	8.90	:	$0.10 < p < 0.20$

Table IX. Final Outcome in Consanguineous and Control Groups

	Consang.	Contr.	$\frac{d^2}{m}$
Lasting, full remission	17	13.8	0.74
Repeated attacks, with full remission	22	9.5	16.45
Full remission, relapse with incomplete rem. . .	10	4.8	0.83
Other forms	–	2.7	
Slight permanent defect	12	22.3	4.76
Moderate permanent defect	13	18.5	1.64
Severe permanent defect	21	28.–	1.75
Observation interrupted before outcome is clear	12	7.4	2.86
Total	107	107	29.03
χ^2 for heterogeneity	15.94	:	$0.02 > p > 0.01$

stressed, as the nature of our material precludes any absolute conclusions as to the mode of inheritance. A forthcoming proband investigation may contribute towards the solution of this problem.

It should be stressed that even in our control material there is naturally a certain amount of "consanguinity", not merely as a result of the in-breeding in the general population, but because many recessive genes are so frequent that even quite unrelated individuals (if such do in fact exist in our country) are bound to have some of them in common. What we know is merely that patients whose parents are first cousins are *more consanguineous* (and consequently more homozygotic) than the average. In view of this the great difference between our two groups is even more striking.

Theoretically the effect of one cousin-mating should in fact not be very great. Preliminary results of our family investigations seem to show, however, that in these families there is a definite tendency towards in-breeding, which may have been more or less traditional for several generations.

Now dominance is not the only factor which has to be taken into account in connection with the problem of consanguinity. Above all the possibility of assortative mating should be considered. We know that there are correlations between psychosis and prepsychotic personality type, and in the epidemiology of psychoses there are strong indications that such personality differentials can lead to social selection which influences migration, marriage, choice of occupation etc. It is conceivable that persons with a predisposition towards affective psychoses have a tendency to marry

within more restricted sozial circles, and an opposite trend may be at work in individuals of schizoid constitution. Migrants are naturally less likely than the average to marry cousins, and it has been shown that in certain migrant groups there is an excess of mental disorders, particularly of schizophrenia.

A further possibility is that in a small community a serious and well-known hereditary taint may lead to in-breeding, because members of such families may feel thrown upon themselves, or perhaps are actually feared as potential partners. In our material this seems to have been the case in a family with *Huntington* chorea, rather prominent, but living in a small community where everybody knew about the disease and most feared it. Not only were the parents of the patient first cousins, but he himself married a cousin, and there were even other cases of consanguineous marriage among the relatives. It is natural that dominant inheritance should be more easily noticed and recognized than recessive. On the other hand, affective psychoses are relatively benign, and it does not seem to be common experience that members of manic-depressive families refrain from marriage or are in any way avoided because of the taint.

Our material stems from the admissions to five different mental hospitals through a period of more than 29 years, and the diagnoses have naturally been made according to varying and heterogeneous principles. This is why the authors have preferred in every case to make a personal revision of the diagnosis made by the hospital—not because this revision is in itself regarded as an improvement, but because the comparison with the control material demands a certain uniformity. Nevertheless this revision of the diagnoses may have led to systematic errors, and it is therefore of interest to present the material even with the original hospital diagnoses. Table X shows that the revision has actually been moderate. The diagnosis was changed in 23 out of the 120 cases, but the net result is that the diagnostic distributions before and after the revision do not differ significantly.

The consanguineous group with unrevised diagnoses should be compared with a corresponding control material, preferably with the entire mass of first admissions to the five mental hospitals during the period of investigation. To simplify the procedure, only every fifth year was counted, giving a presumably representative sample of 2179 first admissions, all of them with the unrevised diagnosis made by the hospital. The right half of table X shows

Table X. In the left half of the table the original and the revised diagnoses of the consanguineous cases are compared. In the right half the consanguineous group is compared with the diagnostic distribution of the total first admissions to the same hospitals, in both cases the diagnoses being the original ones.

	Revised	Original	$\frac{d^2}{m}$	Cons.	Contr.	$\frac{d^2}{m}$
Schizophrenia	49	54	0.47	54	52.1	0.07
Manic-depressive psychosis	26	23	0.39	23	11.2	12.59
Reactive, all types	31	21	4.76	21	24.8	0.58
With mental deficiency	8	11	0.82	11	7.6	1.52
Senile and arteriosclerotic	4	4	0.11	4	10.8	4.28
Epileptic psychoses	4	5		5	2.3	0.26
Other organic	1	4		4	5.3	
General paresis	2	2		2	4.2	
Symptomatic psychoses	–	–	2 00	–	3.2	5.12
Other and indefinite forms	1	2		2	0.8	
Not insane	–	–		–	3.7	
Total	126	126	8.55	126	126	24.42
χ^2 for heterogeneity	4.28 : $0.7 > p > 0.5$			22.40 : $0.01 > p > 0.001$		

that even with this diagnostic classification the consanguineous group differs from the control in several respects. As might have been expected general paresis, symptomatic and senile and arteriosclerotic psychoses are less well represented, while psychoses with epilepsy and with mental deficiency are relatively more frequent. Even using the unrevised diagnoses we find that manic-depressive psychosis is more than twice as frequent as in the control group, while for schizophrenia and reactive psychoses the difference has more or less disappeared (The reactive group is very heterogeneous, but the hospital diagnoses do not make it possible to break it up in sub-groups according to the clinical picture). Generally this is the same picture as was found when revised diagnoses were used, but the excess of manic-depressive psychosis as compared with schizophrenia is somewhat less marked.

Summary

Among 11145 first admissions to five Norwegian mental hospitals were found 126 patients whose parents were first cousins. The rate of consanguinity among the first admissions was found to be 0.9 per cent for patients from cities and from eastern rural districts, while for a western fjord county it was 3.4 per cent.

A comparison between the consanguineous patients and a control group revealed an excess of affective and remittant psychoses at the expense of paranoid and deteriorating forms.

Résumé

Parmi 11 145 malades soignés pour la première fois dans cinq hôpitaux psychiatriques de Norvège, l'auteur a trouvé 126 malades dont les parents étaient cousins germains. Le taux de consanguinité parmi ces malades s'élevait à 0,9 pour cent pour ceux venant des villes et des districts ruraux de l'est, tandis qu'il s'élevait à 3,4 pour cent pour une région située dans un fjord de l'ouest.

Une comparaison entre les malades consanguins et un groupe de contrôle révéla un excès de psychoses affectives et rémittentes aux dépens des formes paranoïdes et progressives.

Zusammenfassung

Unter 11 145 Patienten aus 5 psychiatrischen Kliniken Norwegens fanden sich 126, deren Eltern Geschwisterkinder ersten Grades waren. Bei Patienten aus Städten und ländlichen Bezirken Ost-Norwegens fanden sich 0,9% und bei solchen aus einem westlichen Fjord-Distrikt 3,4% mit blutsverwandten Eltern.

Ein Vergleich zwischen Patienten mit blutsverwandten Eltern und einer Kontrollgruppe ergab einen Überschuß von affektiven und remittierenden Psychosen auf Kosten von paranoiden und verblödenden Formen.

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L'AGE MATERNEL ET LE RANG DE NAISSANCE DANS UN ECHANTILLON DE JUMEAUX

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Introduction

Diverses méthodes permettent d'apprécier l'influence relative de l'âge maternel et du rang de naissance sur un phénomène quelconque.

Certaines n'utilisent que le matériel fourni par l'ensemble des fratries, sans faire appel à un échantillon témoin. Elles consistent à comparer l'âge ou le rang observé à un âge ou un rang théorique, l'autre facteur étant fixé.

Ce sont de telles méthodes qui ont été décrites et utilisées par *L. S. Penrose* dans différentes études et en particulier dans ses travaux concernant le mongolisme.

La deuxième voie requiert l'emploi d'un échantillon-témoin, représentatif de la population générale et auquel est comparé l'échantillon à tester. C'est cette méthode que nous avons appliquée dans le présent travail.

Le matériel

Le matériel que nous étudions est uniquement constitué par l'ensemble des jumeaux suivis depuis 1942 à la Consultation spécialisée pour enfants jumeaux, à la Clinique de Génétique Médicale.

Nous n'avons retenu que les jumeaux pour lesquels le diagnostic de dizygotie et de monozygotie avait pu être établi (par l'emploi des tests habituels) avec certitude. Nous avons ainsi obtenu un nombre

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total de 1072 paires de jumeaux: 441 paires monozygotiques (MZ) et 631 paires dizygotiques (DZ)

Il convient de remarquer que cet échantillon ne concerne que des paires dont les deux membres sont nés viables. Notons de plus que les proportions de Weinberg ne sont pas retrouvées en raison du principe même du recrutement: celui-ci s'est fait en grande partie dans les écoles. Les écoles mixtes étant rares dans la région parisienne, une sélection s'est opérée en faveur des jumeaux de même sexe, dans notre échantillon. Il est probable que pour les jumeaux de même sexe la sélection a joué également en faveur des jumeaux MZ qui sont près d'une fois et demie plus nombreux que les DZ.

L'échantillon témoin a été obtenu en prenant dans le registre des naissances de la Maternité Baudelocque à Paris, toutes les 60ièmes naissances depuis 1942, date de naissance des plus anciens des jumeaux de notre échantillon. Cet échantillon témoin s'étale sur les mêmes années que l'échantillon de jumeaux. Il couvre en particulier les années de guerre qui ont pu modifier dans la population générale le rôle de l'âge maternel et du rang de naissance.

Etude de l'âge moyen

L'âge moyen de la population de jumeaux est supérieur à celui de la population témoin: d = 2,47 ans. La valeur de t pour cette différence est t = 8,71, la différence est donc hautement significative (tableau 1).

Tableau 1. Age maternel moyen

	Jumeaux	MZ	DZ	Témoins
N	1072	441	631	1000
m	29,54	29,06	29,93	27,07
σ	5,84	6,2	5,6	6,72
s	0,18	0,29	0,22	0,21

A l'intérieur de l'échantillon de jumeaux nous avons comparé les jumeaux MZ aux jumeaux DZ. La différence entre les âges moyens dans ces deux groupes de jumeaux est d = 0,87. La valeur de t pour cette différence est t = 2,35 avec $0,01 < p < 0,05$.

Si nous comparons maintenant chacun de ces deux groupes de jumeaux à la population témoin nous avons:

$$d_{DZ} = 2,86 \qquad t = 9,22$$
$$d_{MZ} = 1,99 \qquad t = 5,38$$

On voit donc que les deux groupes contribuent à la différence. Toutefois, l'influence des jumeaux DZ semble plus grande.

Le rapport des naissances gémellaires aux naissances simples a été calculé pour chaque classe d'âge maternel. Le rapport DZ/T augmente progressivement et passe par un maximum pour la classe d'âges 35–38. Pour les jumeaux MZ, le rapport augmente progressivement et la courbe n'a pas la même allure modale (tableau 2).

Tableau 2. Proportions des naissances gémellaires aux naissances simples en fonction de l'âge (MZ et DZ séparés)

Age maternel	DZ n	DZ %	DZ/T	MZ n	MZ %	MZ/T
15–18	6	0,95	0,288	3	0,68	0,206
19–22	49	7,77	0,331	62	14,05	0,598
23–26	129	20,44	0,786	103	23,36	0,898
27–30	158	25,04	1,118	111	25,17	1,124
31–34	151	23,93	1,899	75	17,01	1,350
35–38	96	15,21	1,975	49	11,11	1,443
39–42	40	6,34	1,668	27	6,12	1,610
43–46	2	0,32	0,457	11	2,49	3,56
Total	631	100,00		441	99,99	

Etude du rang moyen

Le rang moyen a été calculé dans les différents échantillons précédemment définis (tableau 3).

Tableau 3. Rang de naissance moyen

	Jumeaux	DZ	MZ	Témoins
N	1072	631	441	1000
m	2,34	2,48	2,13	2,17
σ	1,6	1,7	1,46	1,57
s	0,049	0,068	0,070	0,049

La différence entre les rangs moyens des populations de témoins et de jumeaux d = 0,17 est significative $0{,}01 < p < 0{,}05$.

Les autres comparaisons montrent que cette différence tient uniquement au rang de naissance moyen élevé (m = 2,48) des jumeaux DZ.

En revanche, le rang de naissance moyen des jumeaux MZ n'est pas différent de celui de la population témoin. Ceci apparaît clairement dans les comparaisons:

$$\text{T et DZ: } d = 0{,}31,\ p < 0{,}01$$
$$\text{MZ et DZ: } d = 0{,}35,\ p < 0{,}01$$

Ainsi que pour l'âge maternel nous avons calculé la fréquence des naissances gémellaires par rapport aux naissances simples pour chaque rang de naissance. Le rapport varie peu d'un rang à l'autre pour les jumeaux MZ.

Pour les jumeaux DZ, il existe deux sommets pour les rangs 6 et 8, mais les rapports ont été calculés sur des petits nombres.

Tableau 4. Proportion des naissances gémellaires aux naissances simples en fonction du rang (MZ et DZ séparés)

Rang	DZ n	DZ %	DZ/T	MZ n	MZ %	MZ/T
1	214	33,91	0,762	187	42,40	0,953
2	186	29,48	1,096	136	30,84	1,146
3	106	16,80	1,244	55	12,47	0,924
4	55	8,72	1,194	32	7,26	0,995
5	28	4,44	1,306	16	3,63	1,068
6	19	3,01	1,514	6	1,36	0,775
7	7	1,11		4	0,91	
8	7	1,11		1	0,23	
9	9	1,43		4	0,91	
Total	631	100,01		441	100,01	

Etude de l'âge moyen à rang de naissance égal

La comparaison a été effectuée entre l'échantillon de jumeaux et l'échantillon témoin ainsi qu'entre les jumeaux MZ et les jumeaux DZ. Cette comparaison nous a montré qu'à rang de naissance égal, les jumeaux naissaient toujours de mères plus âgées que les sujets de la population témoin. La différence entre les âges moyens est significative pour les 5 premiers rangs de naissance. Pour le 5e rang $t = 2{,}08$ $p < 0{,}05$. Mais pour le 6e $t = 0{,}14$ (tableau 5).

Pour chacun des 5 premiers rangs de naissance l'examen des résultats montre que la différence entre l'âge maternel moyen des jumeaux et celui des témoins reste sensiblement constante (2,40; 2,26; 2,91; 2,34; 2,48).

En revanche les valeurs de t, calculées pour chaque classe, décroissent de 6,41 à 2,08. Ceci nous semble du à ce que, les classes diminuant d'effectif, les erreurs calculées augmentent. De ce fait, nous pensons que toutes les différences observées sont très significatives et que l'âge maternel moyen des jumeaux est supérieur à celui des témoins, quelque soit le rang de naissance.

Pour le 6^e rang de naissance $t = 1$ et $p = 0{,}35$. Il est possible que cette exception résulte des aléas de l'échantillonnage.

Aucune des comparaisons effectuées entre jumeaux DZ et jumeaux MZ n'est significative (tableau n° 6).

La différence entre les âges maternels moyens ne se fait pas toujours dans le même sens: sur le tableau 6 nous avons affecté du signe — les différences en faveur des jumeaux DZ. On voit donc que si l'âge maternel moyen des jumeaux DZ est supérieur à celui des jumeaux MZ, comme nous l'avons dit plus haut, la différence entre ces âges maternels est très inégalement répartie si l'on maintient constant le rang de naissance. Il paraît du reste bien difficile d'accorder une signification biologique à cette constatation.

Etude du rang de naissance moyen à âge maternel égal

La comparaison effectuée entre les jumeaux et les témoins nous montre qu'à âge maternel égal, le rang de naissance moyen des témoins est habituellement plus élevé que celui des jumeaux à l'exception toutefois de la classe d'âge maternel 39–42 (tableau n° 7).

Au demeurant, aucune des différences trouvées n'est significative sinon celle calculée pour la classe d'âge maternel 31–34: $p = 0{,}01$.

Remarquons qu'il existe une contradiction apparente entre ces résultats et ceux obtenus dans le calcul du rang moyen sans élimination du facteur âge. En effet, dans cette dernière comparaison, le rang de naissance moyen des jumeaux apparaissait supérieur à celui de la population témoin. Si l'on élimine le facteur «âge», la différence entre les rangs de naissance moyens s'annule voire s'inverse. On peut vérifier que la moyenne des rangs calculée après groupement par classes d'âge est bien la même que celle calculée sans groupement (2,331 et 2,335) (tableau n° 8).

La comparaison entre jumeaux MZ et DZ montre qu'à âge maternel égal, le rang de naissance n'est pas significativement différent pour ces deux groupes de jumeaux sauf pour les classes 27–30 et

Tableau 5. Etude de l'âge maternel à rang de naissance fixe

	1		2		3		4		5		6 et +	
	J	T	J	T	J	T	J	T	J	T	J	T
15–18	9 2,24	29 6,51		4 1,49								
19–22	79 19,70	168 37,75	31 9,63	52 19,33	1 0,62	11 8,15		3 4,11		1 2,94		
23–26	133 33,16	132 29,66	62 19,65	69 25,65	21 13,04	38 28,15	12 13,79	15 20,55	3 6,82	4 11,76	1 1,75	2 4,55
27–30	101 25,18	73 16,41	90 27,95	76 28,25	39 24,22	40 29,63	19 21,84	20 27,40	12 27,27	10 29,41	8 14,03	5 11,36
31–34	50 12,46	27 6,07	76 23,61	36 13,38	54 33,54	20 14,82	25 28,74	24 32,87	8 18,18	9 26,47	13 22,81	10 22,73
35–38	22 5,48	11 2,47	51 15,84	23 8,55	25 15,53	13 9,63	19 21,84	5 6,85	8 18,18	8 23,53	20 35,08	17 38,63
39–42	6 1,49	5 1,12	8 2,18	7 2,60	18 11,19	12 8,88	10 11,49	5 6,85	12 27,27	1 2,94	13 22,81	8 18,18
43–46	1 0,29		4 1,24	2 0,75	3 1,86	1 0,74	2 2,30	1 1,37	1 2,27	1 2,94	2 3,51	2 4,55
	401 100,00	445 99,99	322 100,00	269 100,00	161 100,00	135 100,00	87 100,00	73 100,00	44 99,99	34 99,99	57 99,99	44 100,00
m	26,50	24,10	29,66	27,40	32,18	29,27	32,59	30,25	34,04	31,56	35,44	35,31
D	2,40		2,26		2,91		2,34		2,48		0,13	
σ^2	25,40	33,29	11,861	30,470	26,214	32,262	26,214	25,806	29,463	25,482	20,070	21,641
e	0,372		0,39		0,64		0,81		1,19		0,92	

Tableau 6. Etude de l'âge maternel à rang de naissance fixe

	1				2				3				4				5 et +	
	MZ		DZ		MZ		DZ		MZ		DZ		MZ		DZ		MZ	DZ
15–18	3	1,60	6	2,80														
19–22	44	23,52	35	16,35	17	12,50	14	7,52	1	1,81								
23–26	62	33,15	71	33,17	27	19,85	35	18,81	7	12,72	14	13,20	4	12,50	8	14,54	3	1
27–30	50	26,73	51	23,83	39	28,67	51	27,42	13	23,63	26	24,52	6	18,75	13	23,63	3	17
31–34	18	9,62	32	14,95	29	21,32	47	25,27	17	30,90	37	34,90	6	18,75	19	34,54	5	16
35–38	6	3,20	16	7,47	17	12,50	34	18,27	7	12,72	18	17,00	10	31,25	9	16,36	9	19
39–42	3	1,60	3	1,40	3	2,20	5	2,67	8	14,54	10	9,43	4	12,50	6	10,90	9	16
43–46	1	0,54			4	2,94			2	3,62	1	0,94	2	6,25			2	1
	187		214		136		186		55		106		32		55		31	70
m	26,12		26,90		29,29		28,86		32,42		32,01		33,75		33,91		35,6	34,5
D	+ 0,78				— 0,43				— 0,41				+ 0,168				— 1,1	

Tableau 7. Etude du rang

	15–18				19–22				23–26				27–30			
	J		T		J		T		J		T		J		T	
1	9	100	29	87,87	79	71,17	168	71,19	133	57,33	132	50,77	101	37,54	73	32
2			4	12,13	31	27,92	52	22,12	62	27,72	69	26,54	90	33,46	76	33
3					1	0,90	11	4,68	21	9,05	38	14,62	39	14,50	40	17
4							3	1,29	12	5,17	15	5,77	19	7,06	20	8
5							1	0,43	3	1,29	4	1,54	12	4,46	10	4
6											1	0,38	6	2,23	3	1
7									1	0,43	1	0,38			2	0
8													1	0,37		
>8													1	0,37		
Total	9	100	33	100,00	111	99,99	235	100,01	232	99,99	260	100,00	269	99,99	224	10
Rang	1		1,21		1,30		1,37		1,68		1,83		2,18		2,26	
D	0,21				0,07				0,15				0,03			
σ^2					0,22		0,46		1,27		1,18		1,41		1,65	
e					0,06				0,11				0,11			

sance à âge maternel fixe

31–34				35–38				39–42				43–46			
J		T		J		T		J		T		J		T	
		27	21,43			11	14,29			5	13,16				
0	22,12			22	15,17			6	8,96			1	7,69		
		36	28,57			23	29,87			7	18,12			2	28,57
6	33,63			51	35,17			8	11,94			4	30,77		
		20	15,88			13	16,88			12	31,57			1	14,29
4	23,90			25	17,24			18	26,87			3	23,08		
		24	7,14			5	6,49			5	13,16			1	14,29
5	11,06			19	13,10			10	14,93			2	15,38		
		9	7,14			8	10,39			1	2,63				
8	3,54			8	5,52			12	17,90			1	7,69		
		3	2,38			6	7,79			4	10,53				
8	3,54			8	5,52			2	2,99			1	7,69		
		3	2,38			1	1,30			1	2,63				
2	0,88			5	3,45			2	2,99			1	7,69		
		1	0,79			5	6,49								
2	0,88			4	2,76			1	1,49						
		3	2,38			5	6,49			3	7,89			3	42,85
1	0,44			3	2,07			8	11,94						
26	99,99	126	99,99	145	100,00	77	99,99	67	100,01	38	99,99	13	99,99	7	100,00
2,61		3,01		3,15		3,68		4,20		3,63		3,38		5,42	
0,40				0,53				0,57				2,04			
2,19		1,73		3,78		5,81		5,37		4,78		2,88		10	
0,15				0,28				0,42				0,84			

Tableau 8. Etude du rang

	15–18				19–22				23–26				27–30			
	MZ		DZ		MZ		DZ		MZ		DZ		MZ		DZ	
1	3	100	6	100	44	70,97	35	71,42	62	60,20	71	55,04	50	45,05	51	32,2
2					17	27,42	14	28,58	27	26,21	35	27,13	39	35,13	51	32,2
3					1	1,61			7	6,80	14	10,85	13	11,71	26	16,4
4									4	3,88	8	6,20	6	5,41	13	8,2
5									2	1,94	1	0,78	2	1,80	10	6,3
6													1	0,90	5	3,1
7									1	0,97						
8															1	0,6
> 8															1	0,6
Total	3		6		62	100,00	49	100,00	103	100,00	129	100,00	111	100,00	158	100,
Rang	1		1		1,30		1,28		1,65		1,70		1,86		2,40	
D					— 0,02				+ 0,05				+ 0,54			
σ^2					1,26		0,22		1,123		0,908		1,090		2,29	
e					0,15				0,13				0,15			

ce à âge maternel fixe

31-34		35-38		39-42		43-46	
Z	DZ	MZ	DZ	MZ	DZ	MZ	DZ
24,00	21,19	12,24	16,67	11,11	7,50	9,09	
	32	6	16	3	3	1	
38,67	31,12	34,70	35,41	11,11	12,50	36,36	
	47	17	34	3	5	4	
22,67	24,50	14,29	18,75	29,62	25,00	18,18	
	37	7	18	8	10	2	1
8,00	12,58	20,41	9,38	14,84	15,00	18,18	
	19	10	9	4	6	2	
5,33	2,65	4,08	6,25	18,51	17,50	9,09	
	4	2	6	5	7	1	
1,33	4,63	4,08	6,25	3,70	2,50	9,09	
	7	2	6	1	1	1	
	1,33	6,12	2,08		5,00		
	2	3	2		2		1
	1,33	2,04	3,12		2,50		
	2	1	3		1		
	0,66	2,04	2,08	11,11	12,50		
	1	1	2	3	5		
100,00	151 99,99	49 100,00	96 99,99	27 100,00	40 100,00	11 99,99	2
,36	2,74	3,28	3,08	3,96	4,37	3,09	
+ 0,38		— 0,20		+ 0,42			
,35	2,54	3,76	3,805	4,87	5,578		
0,186		0,34		0,56			

31–34 où le rang de naissance des jumeaux DZ est significativement supérieur à celui des MZ. Respectivement nous avons p (27–30) < 0,01 et p (31–34) = 0,05.

Si nous comparons le rang de naissance des jumeaux MZ et DZ à celui de la population témoin nous constatons à nouveau que le rang de naissance des jumeaux est inférieur à celui de la population témoin à l'exception de la classe d'âge 39–42 et également de la classe 27–30 pour les jumeaux MZ seulement.

Ainsi il ressort de notre étude que le taux de la gémellité augmente avec l'âge maternel mais qu'il est peu lié, sinon indépendant, du rang de naissance.

Nous avons cherché à confirmer ces résultats en appliquant une méthode dérivée de celle utilisée par *Penrose* dans son étude sur l'influence de l'âge maternel et du rang de naissance sur le placenta praevia.

Au lieu de calculer, comme cet auteur l'avait fait, l'âge moyen et le rang théorique de nos jumeaux, à partir de l'échantillon étudié; nous avons utilisé notre population témoin et calculé, dans celle-ci, le coefficient de corrélation entre l'âge maternel et le rang de naissance.

Nous avons: $r = 0{,}49$.

Nous avons alors cherché en fonction de ce coefficient quel aurait du être l'âge maternel de nos jumeaux, si le rang de naissance n'avait eu aucune influence sur la gémellité. Cet âge théorique nous est donné selon *Penrose* par la formule:

$$Ac = \sigma_A / \sigma_R \cdot r\,(R_s - R_t) + A_t$$

Ac = âge calculé

σ_A et σ_R représentent la déviation standard pour l'âge et le rang dans l'échantillon témoin,

R_s = le rang de naissance des jumeaux

R_t = le rang de naissance des témoins

A_t = l'âge maternel moyen des témoins

Les comparaisons effectuées donnent:

jumeaux MZ: Ac = 26,99

jumeaux DZ: Ac = 27,72

Les différences entre les âges observés et calculés sont:

jumeaux MZ: 29,06 – 26,99 = 2,07

jumeaux DZ: 29,93 – 27,72 = 2,21

En ce qui concerne le rang, le rang théorique obtenu en éliminant l'influence de l'âge maternel est donné par:

$$Rc = \sigma_R / \sigma_A\, r\,(A_s - A_t) + R_t$$

A_s = Age des jumeaux

D'où il vient:
jumeaux MZ Rc = 2,40
jumeaux DZ Rc = 2,45
Les différences entre les âges observés et calculés sont ici:
jumeaux MZ: D = 2,13 - 2,40 = —0,27
jumeaux DZ: D = 2,48 - 2,45 = +0,03

Ces résultats confirment ceux de notre première analyse. On voit, en effet, que si l'on élimine l'influence du rang de naissance l'âge maternel de nos jumeaux est supérieur à l'âge théorique calculé à partir de la population témoin et l'on remarque que la différence est du même ordre de grandeur pour les jumeaux MZ et les jumeaux DZ.

D'autre part le rang de naissance de nos jumeaux DZ est très sensiblement égal au rang théorique calculé en éliminant l'influence de l'âge.

Le rang de naissance des jumeaux MZ est inférieur au rang théorique, mais cette différence (—0,27) n'est probablement pas significative.

Rapport des naissances gémellaires aux naissances totales

Nous avons calculé ces rapports après groupage des classes, en raison du petit nombre de cas dans chacune d'elles. On remarque pour chaque rang de naissance une augmentation du nombre des naissances gémellaires avec l'âge maternel. Il est difficile de préciser ici si la courbe est modale ou non comme il le semblerait pour les jumeaux DZ, mais non pour les MZ (tableau n° 9).

Tableau 9. Rapport des pourcentages MZ/T DZ/T (en fonction de l'âge).

	1		2		3		4 et +	
— 22		0,43		0,36		0,57		0,79
	0,57		0,6					
23–30		1,24		0,86				
	1,30		1,04		0,56		0,64	
31–38		2,47		1,98		2,12		1,04
			1,54		1,79			
+ de 39				0,80		1,08		1,54
	1,55		1,54		1,89		2,26	

MZ = coin inférieur gauche, DZ = coin supérieur droit.

Quoiqu'il en soit ces résultats montrent encore la nette influence de l'âge maternel sur le phénomène de la gémellité.

Nous avons également déterminé le rapport des naissances gémellaires aux naissances simples en fonction du rang. Ces rapports ne suivent pas la même courbe pour chaque classe d'âge et pour chaque catégorie de jumeaux (tableau n° 10.)

Tableau 10. Rapport des pourcentages MZ/T DZ/T (en fonction du rang).

	− 22	23–30	31–38	+ de 38
1	1,01	1,0	1,04	0,64
	0,98	1,24	1,03	0,95
2	1,22	1,0	1,13	0,6
	1,25	1,03	1,28	0,92
3		0,86	1,37	0,91
		0,58	1,19	0,91
4		0,84	0,79	1,07
			0,90	1,18
5 et +			0,65	1,52
		0,65	0,52	1,09

MZ = coin inférieur gauche, DZ = coin supérieur droit.

Peut-être doit-on noter l'augmentation de ce rapport avec le rang de naissance pour les mères âgées de plus de 30 ans. Encore que pour la classe 31–38 le rapport diminue après le 3e rang. Il est difficile de formuler des conclusions précises à partir de résultats aussi limités.

La comparaison des jumeaux MZ et des témoins ne fait ressortir aucune tendance précise dans l'évolution du rapport étudié, d'un rang de naissance à l'autre.

Discussion

L'augmentation de la gémellité avec l'âge de la mère a été notée dès 1865 par *Duncan* et trente ans après par *Bertillon*.

Il semblait toutefois que l'influence de l'âge maternel ne s'excerçât que sur la gémellité dizygotique, le taux des grossesses monozygotiques en étant indépendant.

D'autre part, dans les travaux initiaux, le départ n'avait pas été fait clairement entre le rôle respectif de l'âge maternel et du rang de naissance.

Certaines études font ressortir toutefois une augmentation de la fréquence des naissances de jumeaux MZ avec l'âge maternel. Ce sont notamment celles de *Trudy Enders* et *Curt Stein* (citée par *Turpin*) et celle de *Norma Mac Arthur*. Nous arrivons aux mêmes conclusions que ces auteurs. Nous constatons en effet une augmentation significative de l'âge maternel moyen des jumeaux MZ et DZ. Cette augmentation se retrouve pour chaque rang de naissance. Enfin, pour chaque rang, la fréquence des naissances gémellaires par rapport aux naissances simples augmente avec l'âge.

L'influence du rang de naissance sur la gémellité semble moins clairement déterminée. *Bertillon* pensait que le rang avait une influence prépondérante. *Duncan* attribuait l'augmentation constatée de l'âge maternel non seulement à un effet spécifique mais aussi à l'élévation du rang.

Yerushalmy et *Sheerer* ont analysé la statistique des naissances gémellaires de New York City pour 1936–37. Ils ont conclu que la fréquence de la gémellité dizygotique était liée indépendamment au rang et à l'âge maternel, mais davantage au premier qu'au second.

Pour *Norma Mac Arthur*, la fréquence de la gémellité monozygotique augmente avec la parité chez les jeunes mères. Mais le rôle spécifique de l'âge maternel est prépondérant.

Quand à la gémellité dizygotique, sa fréquence paraît à cet auteur indépendamment liée à l'âge et au rang. Pour chaque classe d'âge la fréquence augmentant nettement après le deuxième rang.

Dans notre échantillon, l'augmentation apparente du rang de naissance des jumeaux DZ par rapport à celui des naissances simples est liée à l'augmentation de l'âge maternel.

Les comparaisons effectuées à âge égal n'ont pas montré de différence significative entre jumeaux et témoins. Le rôle du rang apparaît donc modeste dans notre échantillon. Si nous retenons d'autre part l'augmentation constatée du rapport des naissances gémellaires dizygotiques aux naissances simples avec la parité, celle-ci n'apparaît pas indépendante de l'âge maternel mais se manifesterait seulement chez des mères de plus de 30 ans.

En ce qui concerne les jumeaux MZ nous n'avons constaté aucune influence du rang de naissance sur la fréquence du phénomène.

En définitive le contraste nous paraît frappant entre l'influence très nette de l'âge maternel aussi bien sur la gémellité MZ que sur la DZ et le rôle – restreint – du rang de naissance.

Remerciements

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Résumé

Les auteurs ont comparé l'âge maternel et le rang de naissance d'un échantillon de 1072 couples gémellaires à une population témoin de même dimension.

Ils ont constaté une augmentation de l'âge maternel moyen aussi bien pour les jumeaux MZ que pour les jumeaux DZ. Cette augmentation est bien une action spécifique puisqu'elle persiste quand le rang de naissance est fixé. La proportion des naissances gémellaires par rapport aux naissances simples augmente avec l'âge, quelque soit le rang de naissance. Mais chez les jumeaux DZ la courbe est modale passant par un maximum pour la classe 35–38.

L'augmentation apparente du rang de naissance constaté chez les jumeaux DZ est secondaire à l'augmentation de l'âge maternel moyen, comme le montrent les comparaisons effectuées à âge fixe.

Aucune influence spécifique certaine du rang de naissances n'a pu être mise en évidence.

Summary

The authors have compared the age of the mothers and the rank of birth in a sample of 1072 twin pairs and in a control series of equal size.

Among the mothers of both uniovular and binovular twins an increase in the mean age has been observed; this increase is of a specific nature as it is found at each birth rank level. Amongst births at each rank the rate of twin births increases with advancing age of the mother. In case of binovular twinning, however, the frequency curve is modal, reaching its maximum at the maternal age of 35–38 years.

The apparent increase with rank of birth, which is observed among binovular twins, is secondary to the augmentation in the mean age of mothers as shown by the comparisons at each age level.

No specific influence of parity was demonstrated with certainty.

Zusammenfassung

Die Verfasser haben das Alter der Mütter und die Stelle in der Geburtenfolge in einer Beobachtungsreihe von 1072 Zwillingspaaren und in einer Kontrollreihe gleicher Größe verglichen.

Unter den Müttern sowohl eineiiger als zweieiiger Zwillinge ist eine Erhöhung des durchschnittlichen Alters beobachtet worden. Diese Erhöhung ist spezifisch, weil sie auch innerhalb jeder Stufe in der Geburtenreihe gefunden worden ist. Die Proportion der Zwillingsgeburten steigt mit dem Alter der Mütter innerhalb jeder Stufe der Geburtenfolge. Für zweieiige Zwillinge erreicht diese Zunahme der Häufigkeit das Maximum in der Altersgruppe von 35 bis 38 Jahren.

Die scheinbare Zunahme mit erhöhter Stellung in der Geburtenreihe, die für zweieiige Zwillinge beobachtet wurde, ist nur eine sekundäre Begleiterscheinung des höheren Alters der Mütter.

Ein Einfluß der Stelle in der Geburtenfolge konnte nicht mit Sicherheit erwiesen werden.

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INCESTUOUS MATINGS AMONG PARENTS OF MENTAL DEFECTIVES[1]

By CARL A. LARSON

Incestuous Matings among Parents of Mental Defectives

During a diagnostic survey of 4,825 mental defectives, born and institutionalized within the South Swedish region of Götaland (*Larson* [1954]), some individuals were observed to have been born to very closely related parents. An attempt was made to ascertain the minimum frequency of incestuous matings leading to birth of children.

Data available from institution files were completed, mainly by means of birth records and parish registers, population and tax registers, and records of children's welfare bureaux. Out of 4,255 matings between 4,251 men and 4,248 women, thus noted, 14 were between individuals so closely related that their cohabitation was criminal according to the law valid until 1937, i.e. at the time of the event, in all cases but one, a nephew-aunt union in 1939. Out of 4,466 individuals from matings between known partners, 14, or 0.3 per cent, issued from the following incestuous matings.

Father–daughter	4 cases
Full sibs	4
Half-sibs	2
Uncle–niece	2
Nephew–aunt	2

[1] This study was aided by a grant to the Institute of Genetics from the Rockefeller Foundation and by a personal grant from the Royal Physiographic Society.

In all of these cases the mating individuals were identified; most of them underwent legal procedure. In 3 additional cases father-daughter matings had been recorded without confession of the partners or other satisfactory proof.

Kinberg, *Inghe* and *Riemer* [1943] estimated the yearly mean of legally proved incests in Sweden at 0.5 per 100,000 inhabitants, one fourth of those judicially recognized incests were between step-father and step-daughter. One such union occurred in the present series of 4,255 matings, it was not ranged with the 14 close kin matings. As not all of the incests referred to by *Kinberg* and co-workers resulted in offspring, an estimate, from their data, of 3 verified incestuous births per 10,000 births in the general population would be rather high. That estimate could be compared with the tenfold rate of verified incestuous births in the present series.

Reactions against perpetrators of incest, promoting early institutionalization of their offspring, could partly explain this difference. *Penrose* [1949] pointed to such factors pertaining to ascertainment through institutional cases. In the present series 5 out of 14 individuals from incestuous matings were morons or of borderline intelligence, 7 were imbeciles and 2 idiots, the proportions between high and low intelligence levels being as in the total series. Out of 4,825 defectives in this series, 2,837 or 58.8 per cent were of rural birth, whereas all but one of the 14 incestuous births occurred to women resident in rural localities. Subnormal or defective intelligence was observed in one or both of the partners in 9 of the 14 incest cases, which was not to be expected, had homozygosity for recessive genes been mainly responsible for the accumulation of incest offspring in institutions. Rather were the incestuous matings symptomatic of the subcultural standard or mental deficiency of the partners.

Summary

14 out of 4,466 matings between parents of institutionalized mental defectives were incestuous.

Résumé

14 cas d'inceste ont été trouvés parmi 4466 unions entre parents d'individus internés pour déficience mentale.

Zusammenfassung

Von 4466 Verbindungen zwischen Eltern von Schwachsinnigen, die in Instituten gehalten wurden, waren 14 inzestuös.

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